DEH-0018

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: UNDHEIM ET AL.)
)
For: MACROLIDES)

CLAIM FOR PRIORITY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby claims the benefits of the filing date of December 20, 2002 to Denmark Application No. PA200201957 under provisions of 35 U.S.C. 119 and the International Convention for the protection of Industrial Property.

If any fees are due with regard to this claim for priority, please charge them to Deposit Account No. 06-1130 maintained by Applicant's attorneys.

Respectfully submitted,

CANTOR COLBURN LLP

By Karen A. LeCuyer
Karen A. LeCuyer, Ph.D.
Registration No. 51,928

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Janice Young-Astwood June 20, 2005
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GB/03/5659

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Kongeriget Danmark

Patent application No.: PA 2002 01957

Date of filing: 20 December 2002

Applicant:
(Name and address)

Alpharma ApS
Dalslandsgade 11
P.O. Box 1736
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Denmark

Title: 10-substituted erythromycin ketolides and methods of making.

IPC: C 07 H 17/08; A 61 P 31/04; C 07 H 17/00

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.

Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

12 january 2004

Helle Schackinger Olesen

Helle Schackinger Olesen

PATENT- OG VAREMÆRKESTYRELSEN

The present invention relates to novel macrolide compounds and salts, esters, solvates or prodrugs thereof; compositions comprising the compound; methods for preparing the compounds; intermediates involved in said methods; and their use inter alia for treatment or prevention of infections in a mammal.

Background

There exists a need for alternative compounds inter alia for the treatment or prevention of diseases and as substrates for synthesising further compounds.

Erythromycin A, and some chemically modified analogues are used in the treatment of bacterial infections. Unfortunately, bacterial strains that are resistant or less susceptible to erythromycins have been identified. Low activity against Gram-negative organisms is another disadvantage with the present family of drugs. Thus there exists a need to improve the activity and profile of the erythromycin family of antimicrobial drugs.

In reports on chemical modifications of erythromycins there are no description of any modification of the 10-methyl group and no bioactivity of such modified molecules have been revealed. The 10-mehyl group has remained inert in reactions so far described. We herein reveal that we have developed a method for chemical transformations of the 10-methyl group in erythromycins into new compounds with valuable antimicrobial agents.

In particular, this invention relates to a new class of macrolide compounds having a novel modification in the C-10 position and provides a new class of 10-substituted 10-desmethyl ketolide derivatives.

Disclosure of the invention

According to an aspect of the present invention the compounds according to claim 1 are provided.

The invention relates to both stereoisomeric forms at the 10-position (R), at the 11-position (R^2) and at C-9 (X,Y), and combinations thereof in the compounds of the invention. This also includes all stereochemical forms within any substituent attached to these positions as well as in R^1.

Detailed disclosure

According to further aspects of the invention, it concerns intermediates, processes, uses and compositions according to claims 2-12. Intermediates or substrates according to the invention may be perceived as being compounds in their own right.

Where protecting groups are used, the invention is not limited to the protecting groups of the examples. Other protecting groups may be used, such as e.g. simple esters, ethers removable by hydrogenolysis or very mild oxidative conditions, mixed acetals, and others.

According to an aspect, the invention concerns any of the processes as represented in any of the schemes, preferably for obtaining a compound according to any of the claims.

According to an aspect, the invention concerns the use of a compound or intermediate according to claims 1-3, for the treatment or prevention of infection in mammals.

According to an aspect, the invention concerns the use of a compound or intermediate according to claims 1-3, for establishing the purity of a compound, preferably a pharmaceutical compound. Not only may compounds (including intermediates and substrates) be used in their own right, but may also be used to measure the purity of a composition, e.g. in cases where an intermediate is not desired in the final composition.

According to an aspect, the invention concerns a compound, intermediate, substrate, process, use or product obtainable by a process according to any of the description, the schemes or the claims.

According to another aspect, the present invention provides a novel method for substitution in the C-10 methyl group. Thus treatment of erythromycin A (1) (Scheme 1) with 10% HCl in ethanol provided the descladinose unsaturated spiroacetal 2 as described in the literature and named erythralosamine. [Flynn, E. H.; Sigal, M. V.; Wiley, P. F.; Gerzon, K.; *J. Am. Chem. Soc.* **1954**, *76*, 3121-3131]. We have confirmed its chemical structure by a single crystal X-ray analysis.

Scheme 1

Chemoselective *N*-oxidation of the spirane **2** was carried out using H_2O_2 as the oxidising agent in methanol at room temperature. The product was the desired *N*-oxide **3** in close to quantitative yield. The *N*-oxide moiety can be regarded as a protected form of the tertiary amino group for a subsequent chemoselective reaction in the 10-methyl group. The bromination was effected by NBS in acetic acid at room temperature. When bromination was attempted with the amine **2** without the protection by the *N*-oxide function, several products were formed. The structure of the bromination product **4** has been verified by a single crystal X-ray analysis. Deprotection with removal of the *N*-oxide function was effected by triphenylphosphine under reflux in THF. The product was the 10-bromomethyl derivative **5**. Therefore both the latter, and its *N*-oxide bromomethyl precursor **4**, have been substrates (or intermediates) for the subsequent reactions. The 2',3-hydroxy groups in structure **5** are accessible for reactions. Structure **5a** shows silyl ether formation.

Scheme 2

In another aspect of this invention for the preparation of key intermediates as substrates for the target compounds, the 3-ketolide **8** was prepared as shown in Scheme 2. For many reactions it was necessary to protect the reactive 2',3-hydroxy groups in structures **2**. Therefore a number of silyl ethers **2a-2c** have been prepared as intermediate reactants.

The substrate was erythralosamine **2**. Selective protection of the 2'-OH group, as an acetyl derivative **6**, was achieved using acetic anhydride with triethylamine. Corey-Kim oxidation of the 3-OH group provided the 3-ketolide **7**. Deprotection of the 2'-OH group was by methanol at room temperature. The ketolide **8** (R = Me) can be oxidised to its *N*-oxide **9** using hydrogen peroxide (*vide supra*) and brominated to furnish the bromomethyl derivative **10**. Phosphine deoxygenation of the *N*-oxide provides the amine **11**. The bromomethyl ketolide **10** is also available by oxidation of the alcohol **5**. *eg.* under Corey-Kim or related conditions.

Scheme 3

Carbylations by cross-coupling reactions are shown in Scheme 3. The *N*-oxide **4** was the substrate for the coupling under Stille conditions with tributyl(2-furyl)stannane, tris(2-furyl)phosphine (TFP), $Pd_2dba_3.CHCl_3$ in NMP at 80 °C to furnish a furyl derivative which was isolated in 51% yield. Under these conditions concurrent phosphine deoxygenation of the *N*-oxide function occurred. The product was the amine **13**. The substrate for the phenylation

reaction was the amine **5**. Satisfactory cross-coupling under the same conditions with tributylphenylstannane gave the 10-benzyl derivative **12** in 60% yield. By these reactions we have shown that either the amine **5** or the *N*-oxide **4** can be the substrate for cross-coupling reactions.

Optionally, a triple bond derivative may be produced. In the simplest case phenylacetylene has been coupled under Stille conditions to provide the alkyne **14**. Sonogashira methodology would provide the same product.

A target in this work has been the prepation of the 10-ethyl derivative as the *e.g.* silyl protected derivative **15**. The reaction has been successfully achieved using trimethylaluminum under palladium-mediated catalysis with the silyl protected substrate **5a** as shown in Scheme 3. The methylated product **15** was obtained in high yield, 84%. Simple silyl deprotection provides the parent dihydroxy compound.

Scheme 4

A functionalized alkene **16** has been introduced under Stille conditions as shown in Scheme 4. The tin reagent was tributyl(1-ethoxyethenyl)stannane. The desired coupling product **16** was isolated in 54% yield. Acid catalysed cleavage of the vinyl ether provides the corresponding methyl ketone **17**.

Scheme 5

Either bromo compound **4** or **5** under hydrolytic conditions will furnish the corresponding hydroxymethyl derivative indicated in Scheme 5. The hydrolysis product **18** from the amine **5** is shown. As an allylic alcohol **18** is selectively oxidised, first to the aldehyde **19** that can be further oxidised to the carboxylic acid **20** and subsequently converted into new derivatives via the carboxy function. Alternatively, the aldehyde **19** is converted into a ketone **22** via adduct **21** formation with an organometallic reagent and a subsequent oxidation.

In this manner the 10-methyl group has been functionalised to aldehyde, ketone and carboxylic acid carbonyl groups for further manipulations towards desired derivatives.

Scheme 6

In Scheme 6 are outlined transformations of 10-carbonyl substituents into five- and six-membered heterocycles at C-10. Aryl derivatives are similarly prepared by ring forming reactions. In this case the products are drawn as heteroaryl derivatives **24** and **25**. The

reactions will in most cases run via a dihydro or even tetrahydro heterocycle that can be further oxidised and aromatised by standard methodology.

Scheme 7

An aldehyde or ketone in the 10-position as in structure **26** (Scheme 7) are suitable substrates for

the introduction of alkenes by the family of Wittig reactions, or related reactions.

Alternatively, the polarization in this reaction can be reversed in which case the bromomethyl substrate must be converted into an ylide for reactions with appropriate aldehydes and ketones to form the same alkenes **27**. It will be recalled, however, that complete chemoselectivity was achieved for *N*-deoxygenation of the bromomethyl derivative **4** using tris(2-furyl)phosphine or triphenylphosphine (Scheme 1). Therefore ylide formation requires stronger reaction conditions or more reactive phosphines or phosphites.

Scheme 8

According to another aspect of the invention, heterosubstituents are substituted into the 10-methyl group shown in the case of the bromide **5** in Scheme 8. Structure **28** represents ether and sulfide derivatives that may be formed in reactions with the bromide **5** and metal olates or thiolates. Both alkyl and aryl derivatives become available in this manner. When the bromide **5** in a first step has been converted into an alcohol **18** in Scheme 5 or the corresponding thiol, the same products **28** are available by alkylation reactions

The methyl ethers **29** would be important synthetic intermediates to provide compounds with a minimum of structural changes from the bioactive erythromycins.

A convenient method for the preparation of 10-methylamino derivatives, is to react the bromide **4** or **5** with an amine. The amination can be run either with the free amine **5** or its *N*-oxide **4**. In the reaction with benzylamine, the amine **5** was the substrate used to provide the benzylaminomethyl derivative **30**. With *p*-chloroaniline in a preliminary experiment, the substrate was the *N*-oxide **4** which furnished the anilino derivative **31**

In order to provide 9-oxo derivatives, the 9-acetal function is to be opened under acidic conditions using catalysis. Due to high resistance towards the acidic conditions tried indirect methods for acetal cleavage are also to be used.

Scheme 9

Scheme 9 outlines some reactions on saturation of the carbon-carbon double bond. After saturation modified reactivity will be realized in chemical transformations at C-9. Besides catalytic hydrogenation, diboron addition can be used to provide the adduct **33**. Substituted boron hydride reagents failed because of serious steric shielding. When the diboron adduct **33** was treated with a carboxylic acid, in this case acetic acid, C-protonation gave the product **34**. Oxidation of the 3-hydroxy derivative **35** to its ketolide **36** can be effected by several reagents. A suitable process involves selective *O*-acetyl protection of the 2'-OH group. The macrolide aglycone hydroxy groups are less reactive for steric reasons. Oxidation of the sugar protected macrolide takes place selectively in the 3-position to furnish the corresponding 3-ketone. The acetyl protecting group is removed by methanol treatment with formation of the product **36**.

Scheme 10

Erythromycins carry a hydroxy group at C-11. In the present series a hydroxy group at C-11 can be reintroduced by treatment of the diborane adduct **33** with hydrogen peroxide under alkaline conditions (Scheme 10). For steric reasons adduct formation is expected to occur from the less shielded α-face thereby providing a compound **37** with stereochemistry of the hydroxy group as in erythromycins. A large excess of the oxidising agent is used in generating the alcohol. Concurrent oxidation of the amino group therefore occurs. The resultant *N*-oxide, however, is readily and cleanly deoxygenated on treatment of the product with triphenylphosphine, the product being structure **37**.

In the subsequent reaction the acetal function at C-9 has to be cleaved and the 3-OH group oxidised to its ketone **39** as outlined in Scheme 10.

Scheme 11

In an alternative oxygen insertion reaction, epoxide formation was successfully achieved using *m*-chloroperbenzoic acid as shown in Scheme 11. The product is the *N*-oxidised structure **40**. *N*-Deoxygenation occurred readily by heating the latter with triphenylphosphine at reflux temperature in THF. The product was the amine epoxide **41**. In the subsequent reaction step, the epoxide **40** can be rearranged to the 11-ketone **42** by Lewis acid catalysis or under the influence of palladium catalysis and reflux conditions in toluene. Various catalytic hydrogenation procedures or metal hydrides can be used to reduce the 11-keto function to a hydroxy group. The choice of reducing conditions will determine the prevalent hydroxy epimer being formed. Cleavage of the 9-acetal and oxidation of the 3-hydroxy group are the next steps to be carried out as above. Alternatively, hydrolytic cleavage of the 9-acetal function can be carried out at the level of the 11-ketone **42** before reductions.

Scheme 12

Erythromycins based on an oxime function in the 9-position have been commerciallised. A classical synthesis of analogues based on the intermediate substrate **45** is outlined in Scheme 12. Oxime formation by treatment with hydroxylamine provides the oxime **46**. The oxime oxygen is alkylated under strongly basic conditions to provide the *O*-alkyl oxime **47**. A subsequent oxidation as carried out above, provides the desired 3-ketolide **48**.

Scheme 13

Scheme 13 gives an outline of the preparation of 9-oxo-6-OMe-3-ketolides **52**. The 9-oxime is protected by reactions as above leading to the *O*-protected oxime **49**. The 6-OH group can be *O*-methylated under strongly basic conditions to furnish the 6-methoxy derivative **50**. Subsequently, the oxime function is removed (*vide infra*) to furnish the 9-oxo derivative **51**. A subsequent oxidation provides the 3-ketolide **52** as a target compound.

Scheme 14

A more detailed synthesis of a 6-*O* allyl derivative **59** is outlined in Scheme 14. Oximation under standard conditions provides the substrate **53** which is protected as an oxime mixed acetal **54** under experimental conditions related to published methodology. This substrate is allylated under strongly alkaline conditions as shown in Scheme 14. The product is the 6-allyloxy derivative **55**. Subsequently, the oxime protecting function is removed. In the first step cleavage of the acetal function is effected by acetic acid to furnish the oxime **56**. The N-O bond is cleaved by bisulfite-formic acid and the resultant imine hydrolysed by aqueous ethanol at elevated temperature to furnish the 9-ketone **57**. Before the oxidation of the 3-hydroxy function, the sugar 2'-hydroxy group has to be protected, in this case by selective acetylation. The oxidation can be effected by several methods including the Corey-Kim oxidation, the Dess-Martin oxidation, Jones oxidation and the Pfitzner-Moffat oxidation to furnish the 3-ketolide **58**. The Corey-Kim oxidation is shown in Scheme 13.
Among other methods, substitution in the allylic moiety can be effected under Heck conditions to furnish target compounds **59**.

Scheme 15

The same oxime protection has also been used in reported 6-*O* methylation work. In clarithromycin work strongly basic solution of aqueous KOH was used. In Scheme 15 this is shown for a transfomation of structure **54** to its 6-methoxy dervative **60**. Subsequently, the oxime protection is removed as discussed in Scheme 14.

Scheme 16

In Scheme 16 shows oxime protection by analogy to literature for the preparation of clarithromycin. The oxime oxygen in substrate **46** is alkylated by 2-chlorobenzyl chloride to furnish structure **62**. TMS-protection is used for the 2'-hydroxyl group in the sugar and in the

3-position, structure **63**. 6-*O*-Methylation is effected by methyl iodide in DMSO-THF with sodium hydroxide as base. The product will be the 6-methoxy derivative **64**. Removal of the benzyl function by hydrogenolysis over palladium on charcoal provides the oxime **61**. Reductive hydrolysis as above yields the 9-ketone **65**. Protection of 3'-OH is by an acetyl function as in structure **66**. Oxidation of 3-OH and acetyl removal by methanol is effected with the same procedure as above. The product is the ketolide **46**.

Scheme 17

2-Substituted ketolides are potentially useful analogues, in particular 2-halogeno derivatives with emphasis on 2-fluoro derivatives. Fluorine can be introduced by an electrophilic substitution on an enolate of the ketolide. The reaction is exemplified by the series shown in Scheme 17, but the fluorination can also be carried out at later steps in a reaction sequence.

Scheme 18

Several ketolide drug candidates are 11,12-cyclic carbamates. The present invention also includes cyclic carbamate structures. One such preparation starts with structure **70** in Scheme 18. Reaction with carbonyldiimidazole leads to the carbonyl activated urethane **71**. The latter, when reacted with an amine or ammonia forms an 11,12 cyclic carbamate **72**. When the *N*-substituent is hydrogen, *N*-alkylation reactions under basic conditions will provide derivatives of type alkyl-heteroaryl. Alternatively, the side-chain is anchored to the amino nitrogen before it is involved in cyclic carbamate formation to furnish structures **72**.

In another series, the amino nitrogen is part of a hydrazine structure or hydrazine itself as shown in the formation of the hydrazide **73** in Scheme 18. A subsequent cyclisation provides the 11,12-cyclic carbazate **74**, probably as a mixture of epimers at C-10. Epimerisation to the natural configuration can take place under the basic conditions caused by excess of hydrazine. The hydrazone **75** is probably an intermediate in a subsequent reductive alkylation with sodium cyanoborohydride and an aldehyde corresponding to the desired side-chain product **76**.

Scheme 19

In Scheme 19 substrate **77** is available by a Stille coupling or a Sonogashira coupling between one of our 10-bromomethyl substrates and a terminal alkyne. In a reaction with palladium diacetate together with triphenylphosphine, initial adduct formation over the triple bond leads to intermediate **78**. A Pd-effected cyclisation reaction subsequently occurs. The

hydridopalladium elimination from the cyclisation adduct requires a *cis*-arrangement of the outgoing substituents which means that double bond isomer **79** is expected. In this manner pharmacophoric groups, as in the new ketolides, may be anchored through the new ring structure to the macrolide. The annulation may also affect the conformational preferences of the macrolide ring in a manner that facilitates hydrolytic cleavage of the acetal. In an atmosphere of carbon monoxide CO insertion leads to annulated six-membered ring derivatives indicated by structure **80**, or in its more stable phenolic form **81**.

A bromomethyl substrate can also be made to react with a geminal diheterofunctional-C_1 reagent. Such reagents could be thiourea or its equivalents, urea or its equivalents, guanidins or its equivalents as indicated in Scheme 20. Of special interest are reagents derived from amidine that will provide annulated pyrimidine derivatives **88** carrying a pyrimidine 2-substituent for additional manipulations.

With thiourea substitution at the bromomethyl carbon by the sulfur is to be expected. The initially formed onium salt **84** can then react further by attack at the acetal carbon with structure **85** as an intermediate. The opening could also take another course resulting in liberation of the 6-hydroxy group (not drawn). In structure **87** both hydroxy groups have been set free. When an amidine was used instead, the annulated dihydropyrimidine **88** would be provided.

If the initial cyclisation instead takes place over the double bond, structure **84** would be the initial product.

Scheme 21

When the reagent is a hydroxylamine or hydrazine, five-membered heterocycles can be formed. Scheme 21 shows some reactions using reagents derived from hydroxylamine. Oxygen has been introduced at the allylic carbon in structure **89**. The nitrogen must be protected for the oxygen to

be the nucleophile. An appropriate reagent in this case is an aldoxime. Mild acid hydrolysis will furnish the aminoxy derivative **90**. Cyclisation under acid catalysis takes place towards the acetal carbon with formation of the cyclic oxime **91** that is an annulated dihydroisoxazole derivative. If desireable, the latter is readily cleaved by hydrogenolysis to provide the hydroxymethyl derivative **92**.

Scheme 22

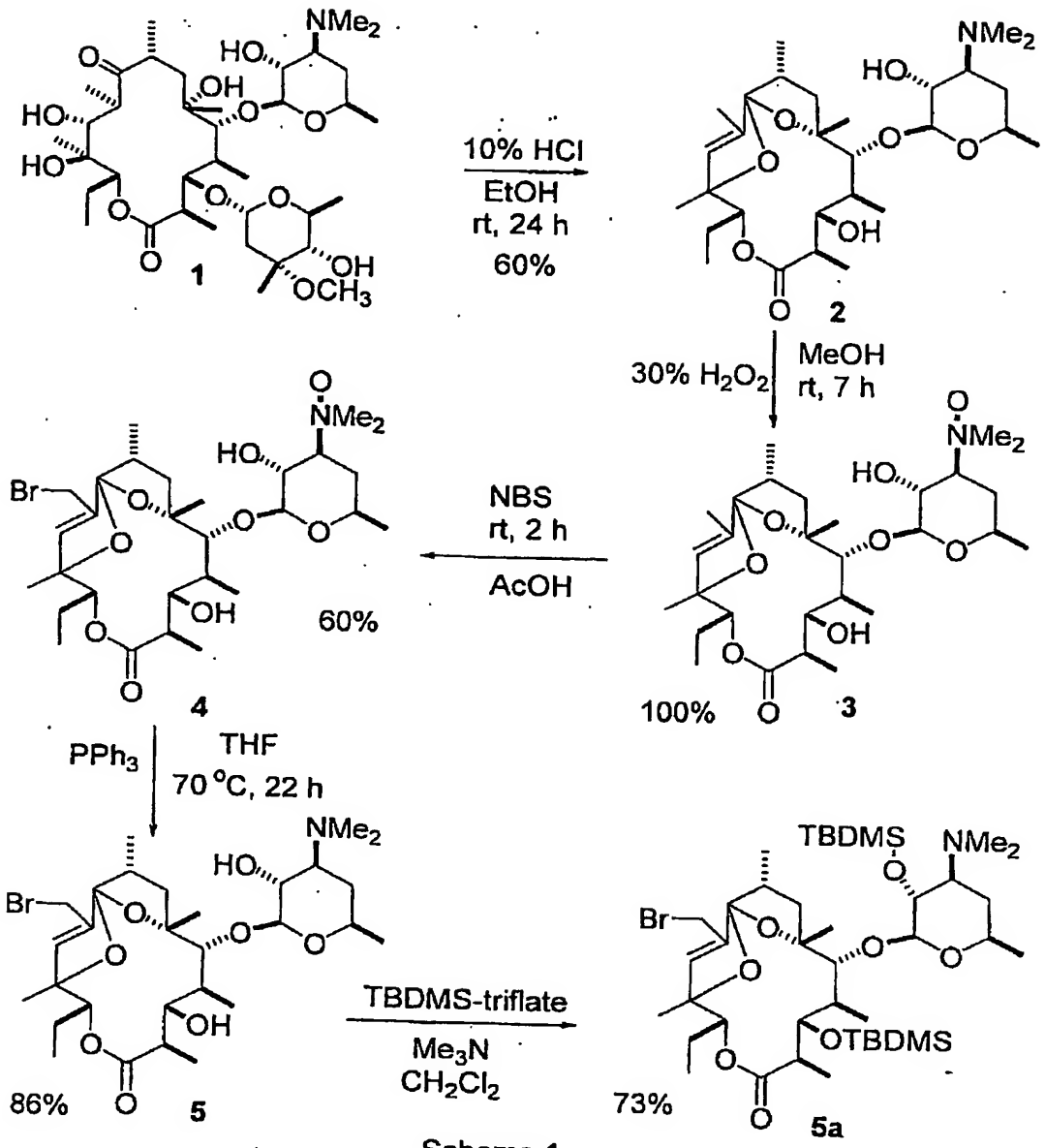
When the cyclisation takes place over the carbon-carbon double bond, a tetrahydroisoxazole **93** is obtained as in Scheme 22. The isoxazole can be cleaved by hydrogenolysis, or as shown, be *N*-alkylated as in structure **94**. Further manipulations are indicated from structures **95**.

Scheme 23

Similar reactions with hydrazines are shown in Scheme 23. Allylic *N*-alkylation provides structure **96**. Acid catalysed cyclic hydrazone formation at the acetal carbon is expected to furnish the dihydropyrrazole derivative **97**. The latter can be further manipulated starting by an *N*-alkylation reaction to provide structure **98**. Hydrogenolysis can be used to cleave the nitrogen-nitrogen bond as in structure **99**.

Scheme 24

In Scheme 24 cyclisation over the carbon-carbon double bond is shown to lead to the tetrahydropyrrazole **101** that can be further manipulated as indicated in structures **102** and **103**.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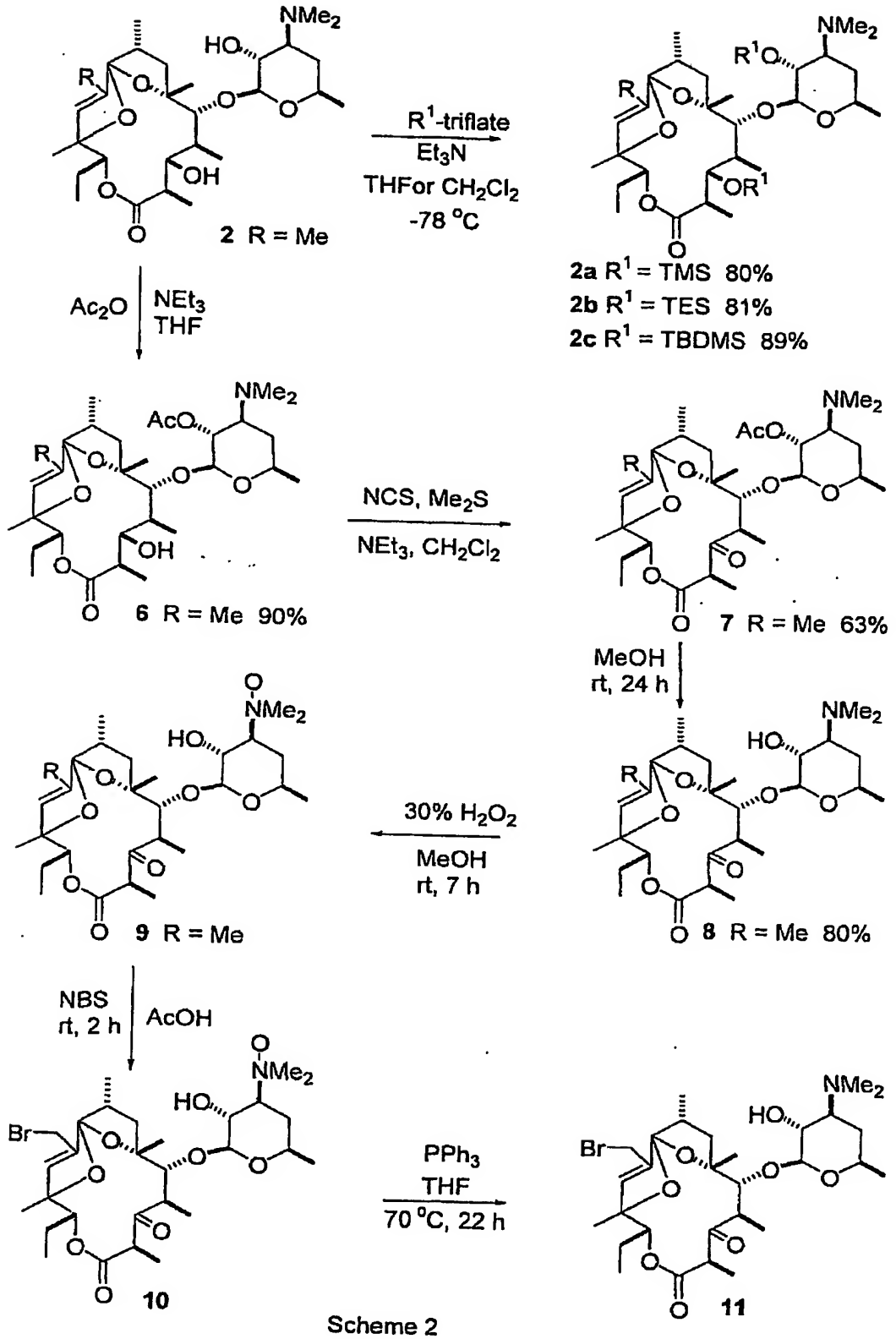
HO
OH
HO
HO
O
O
OH
OCH3
1
10% HCl
EtOH
rt, 24 h
60%
2
30% H2O2
MeOH
rt, 7 h
3
100%
NBS
rt, 2 h
AcOH
4
60%
Br
PPh3
THF
70 °C, 22 h
5
86%
TBDMS-triflate
Me3N
CH2Cl2
TBDMS
5a
73%
OTBDMS

Scheme 1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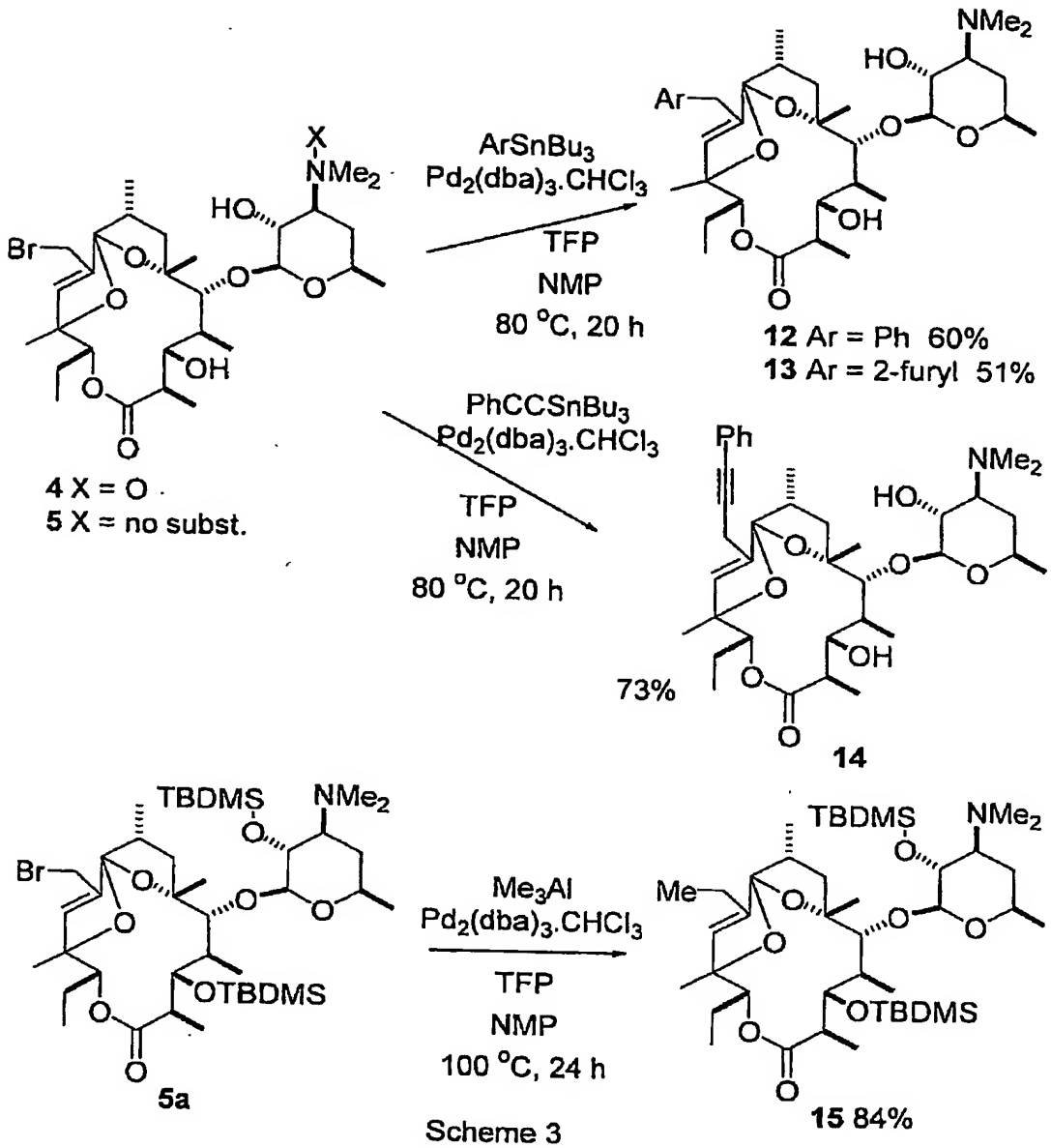
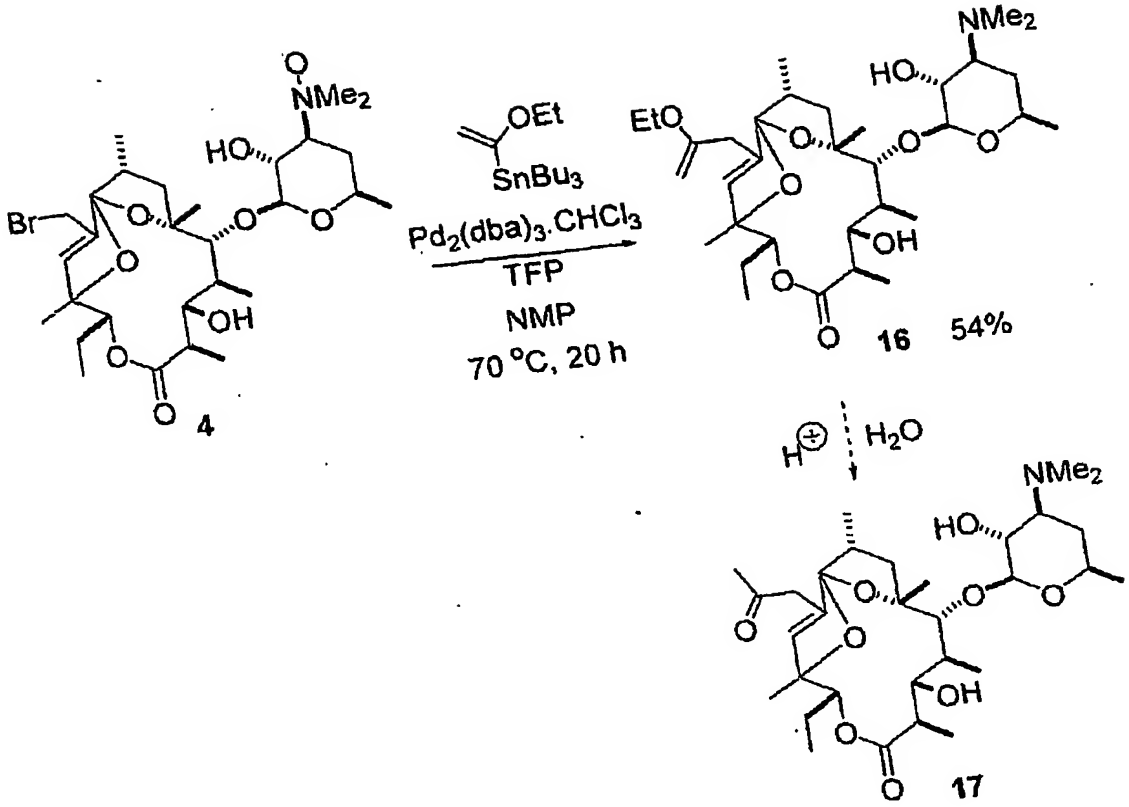
R
O
OH
2 R = Me
R1-triflate
Et3N
THFor CH2Cl2
-78 °C
R1O
OR1
2a R1 = TMS 80%
2b R1 = TES 81%
2c R1 = TBDMS 89%
Ac2O
NEt3
THF
AcO
6 R = Me 90%
NCS, Me2S
NEt3, CH2Cl2
7 R = Me 63%
MeOH
rt, 24 h
8 R = Me 80%
30% H2O2
MeOH
rt, 7 h
9 R = Me
NBS
rt, 2 h
AcOH
Br
10
PPh3
THF
70 °C, 22 h
11

Scheme 2


ArSnBu3
Pd2(dba)3.CHCl3
TFP
NMP
80 °C, 20 h
12 Ar = Ph 60%
13 Ar = 2-furyl 51%
4 X = O
5 X = no subst.
PhCCSnBu3
Pd2(dba)3.CHCl3
TFP
NMP
80 °C, 20 h
73%
14
Me3Al
Pd2(dba)3.CHCl3
TFP
NMP
100 °C, 24 h
5a
15 84%

Scheme 3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Br
O
OH
4
OEt
SnBu3
Pd2(dba)3.CHCl3
TFP
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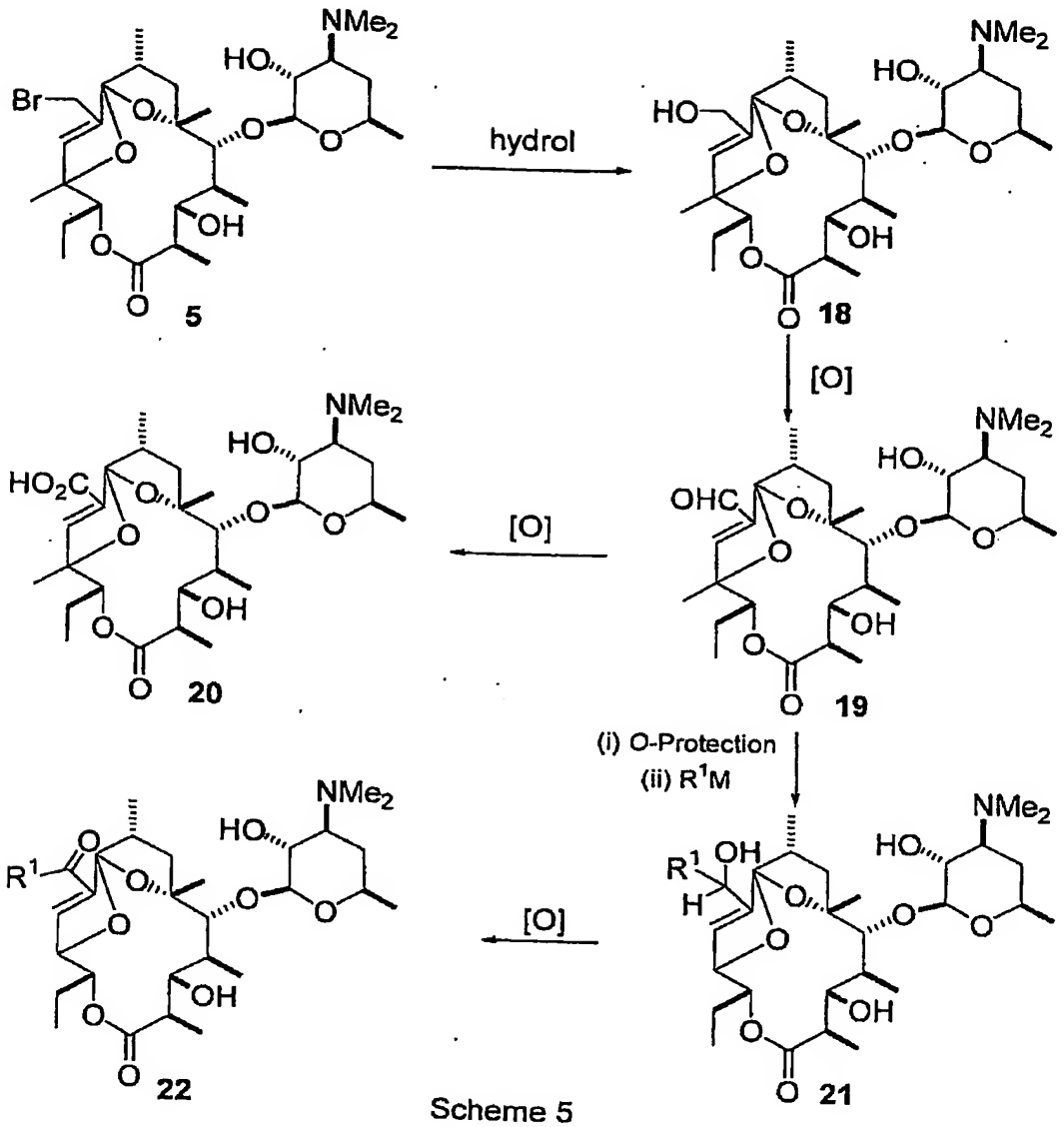
70 °C, 20 h
EtO
16
54%
H⊕
H2O
17

Scheme 4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HO
Br
O
O
O
OH
O
O
5
hydrol
HO
18
[O]
OHC
19
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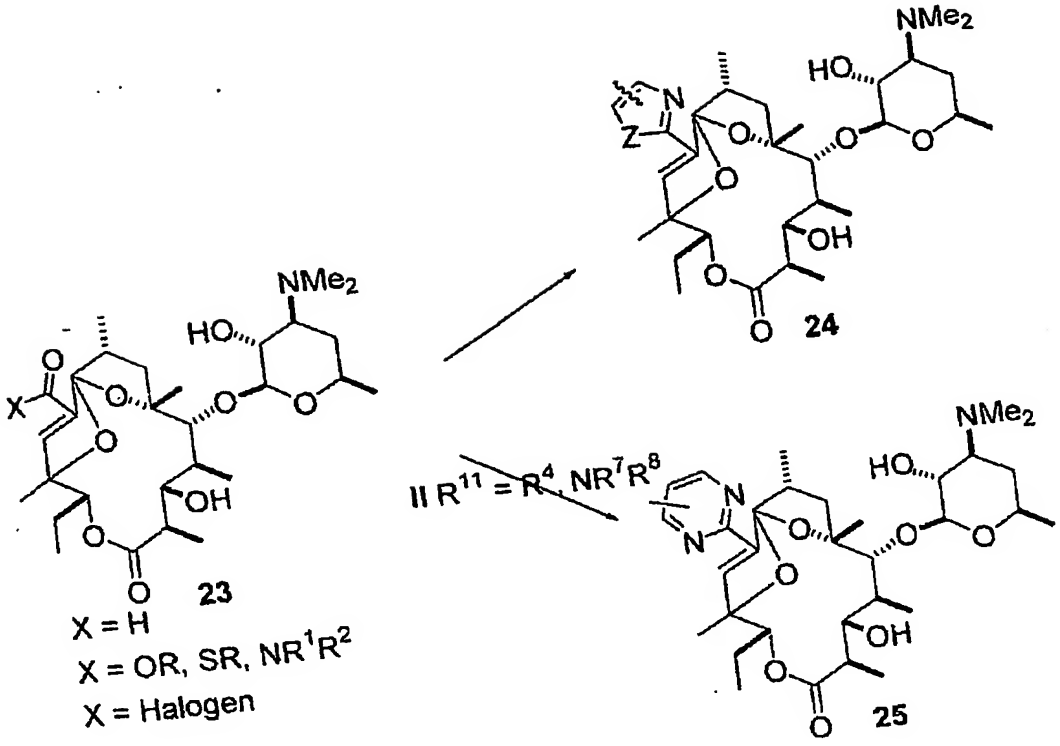
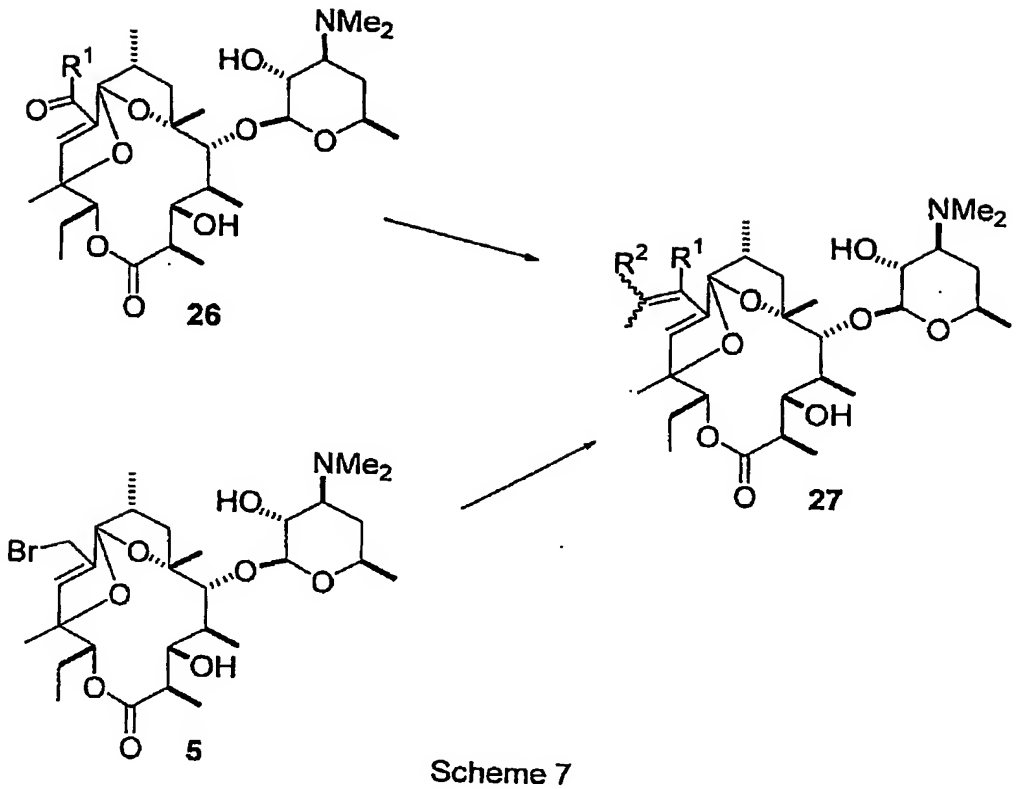
(ii) R1M
HO2C
20
[O]
R1
OH
H
21
[O]
22

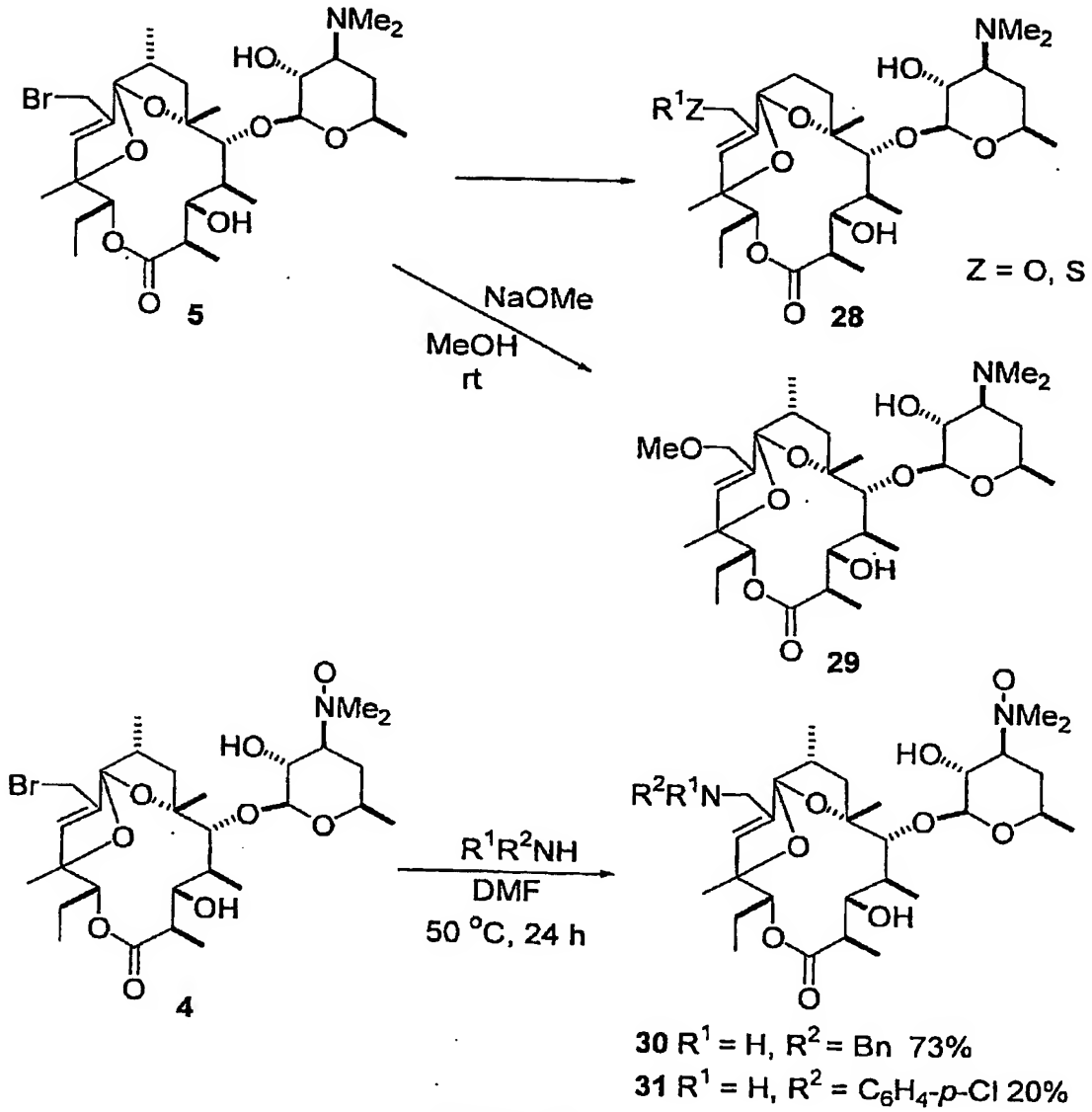
Scheme 5


NMe2
HO
N
Z
O
OH
O
24
X
23
X = H
X = OR, SR, NR1R2
X = Halogen
II R11 = R4, NR7R8
25

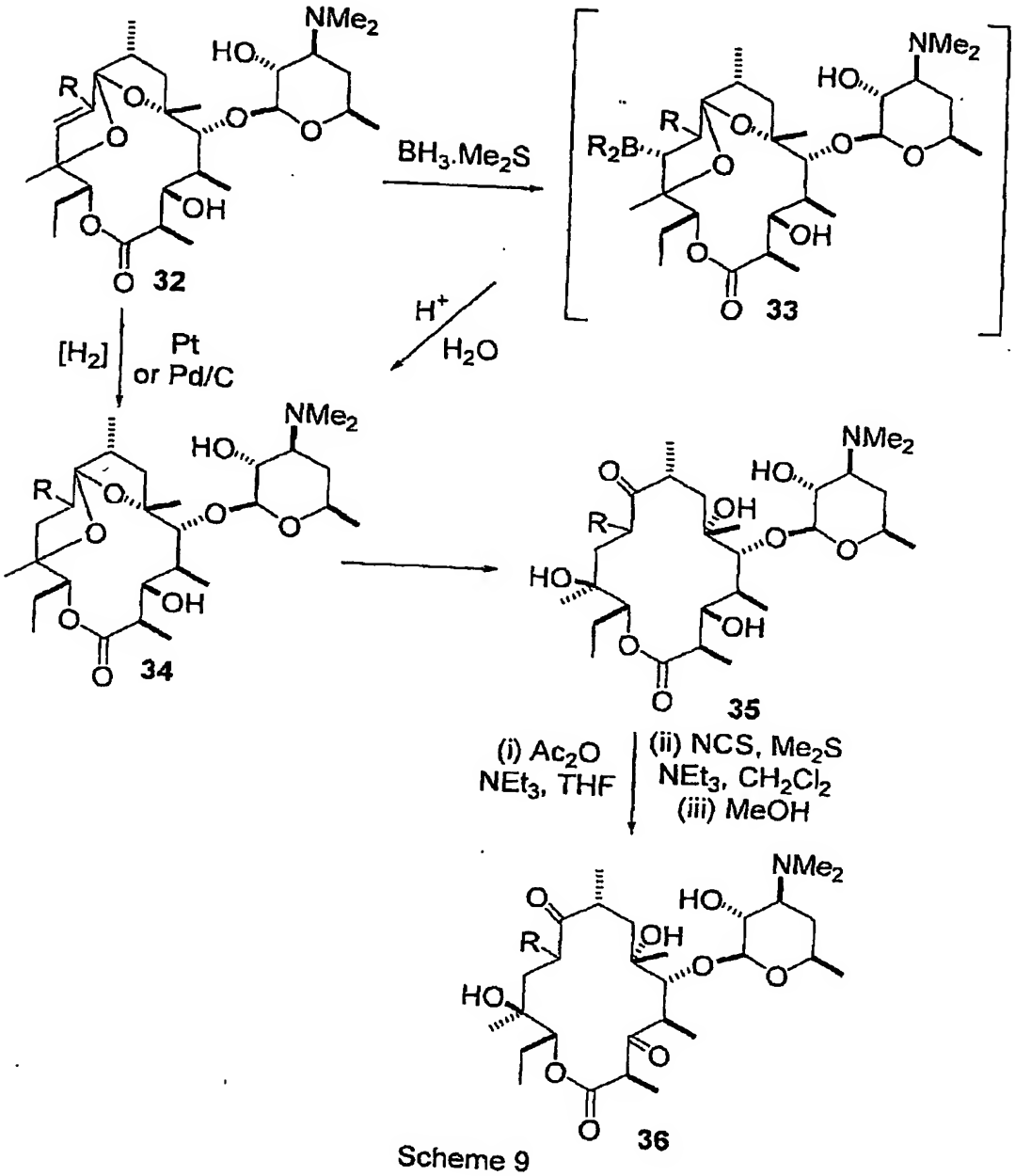
Scheme 6



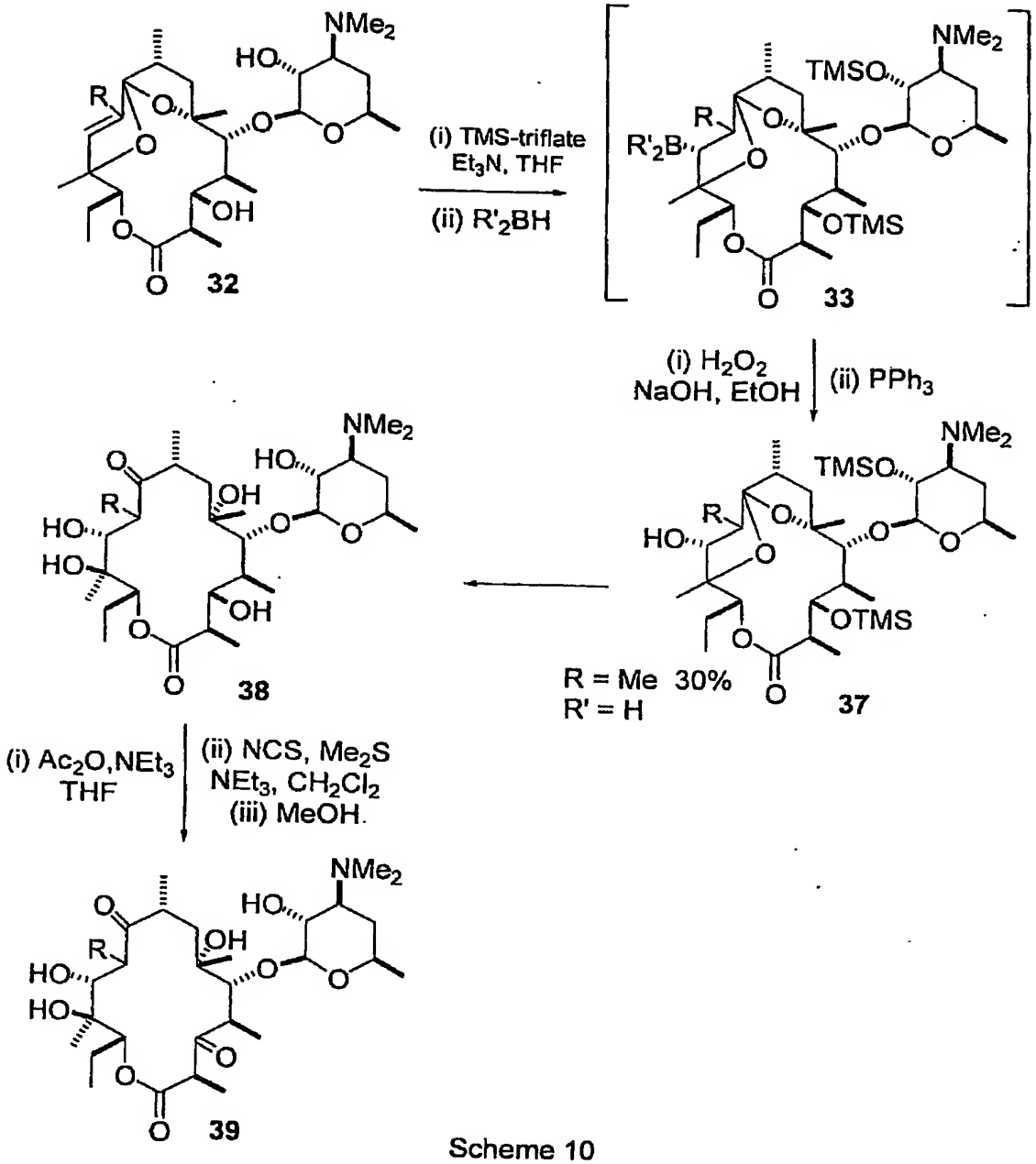
Scheme 7


NMe2
HO
Br
O
OH
5
R1Z
28
Z = O, S
NaOMe
MeOH
rt
MeO
29
O
NMe2
4
R1R2NH
DMF
50 °C, 24 h
R2R1N
30 R1 = H, R2 = Bn 73%
31 R1 = H, R2 = C6H4-p-Cl 20%

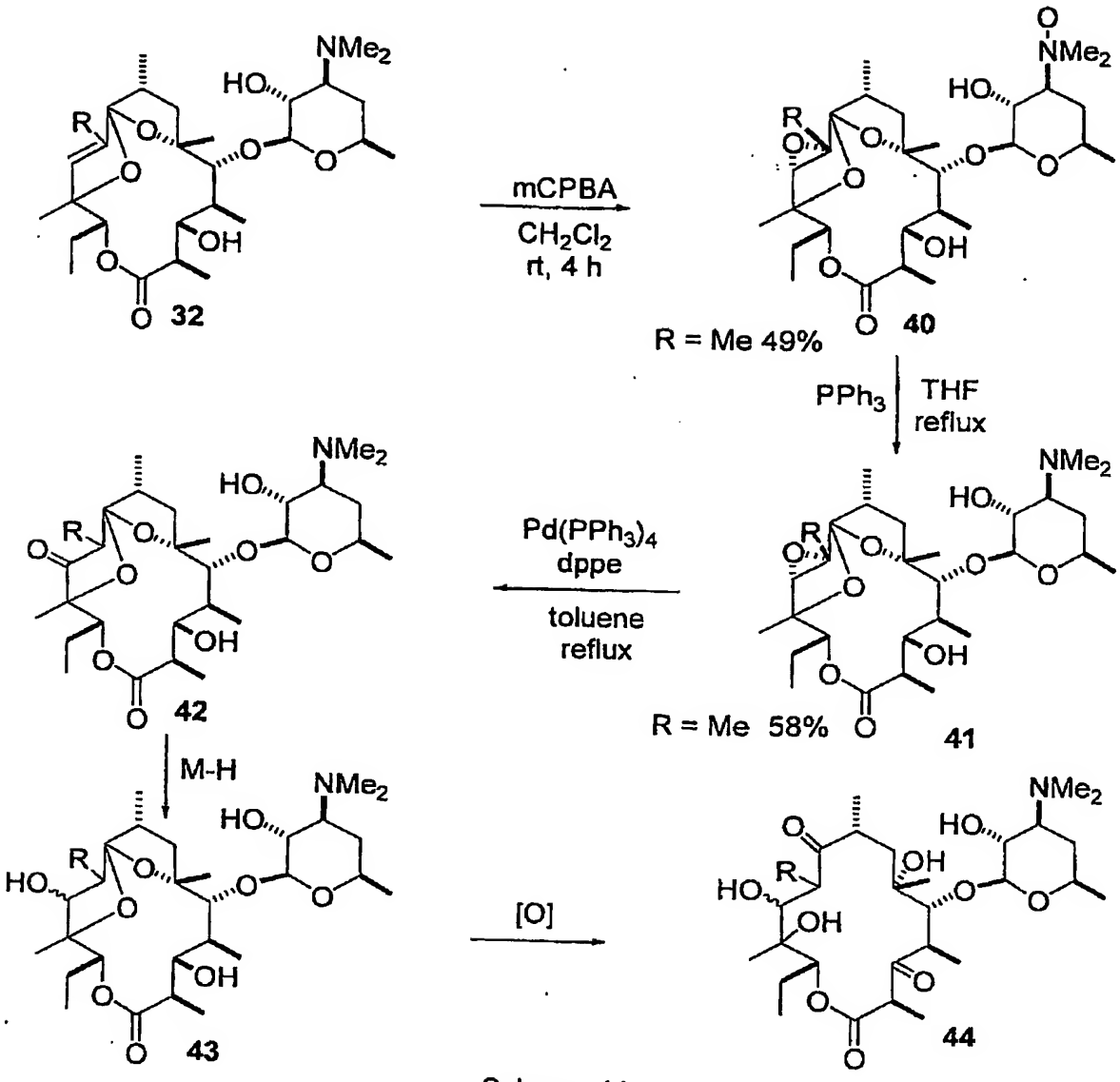
Scheme 8


NMe2
HO
R
O
OH
32
BH3.Me2S
R2B
33
H+
H2O
[H2]
Pt
or Pd/C
34
35
(i) Ac2O
NEt3, THF
(ii) NCS, Me2S
NEt3, CH2Cl2
(iii) MeOH
36

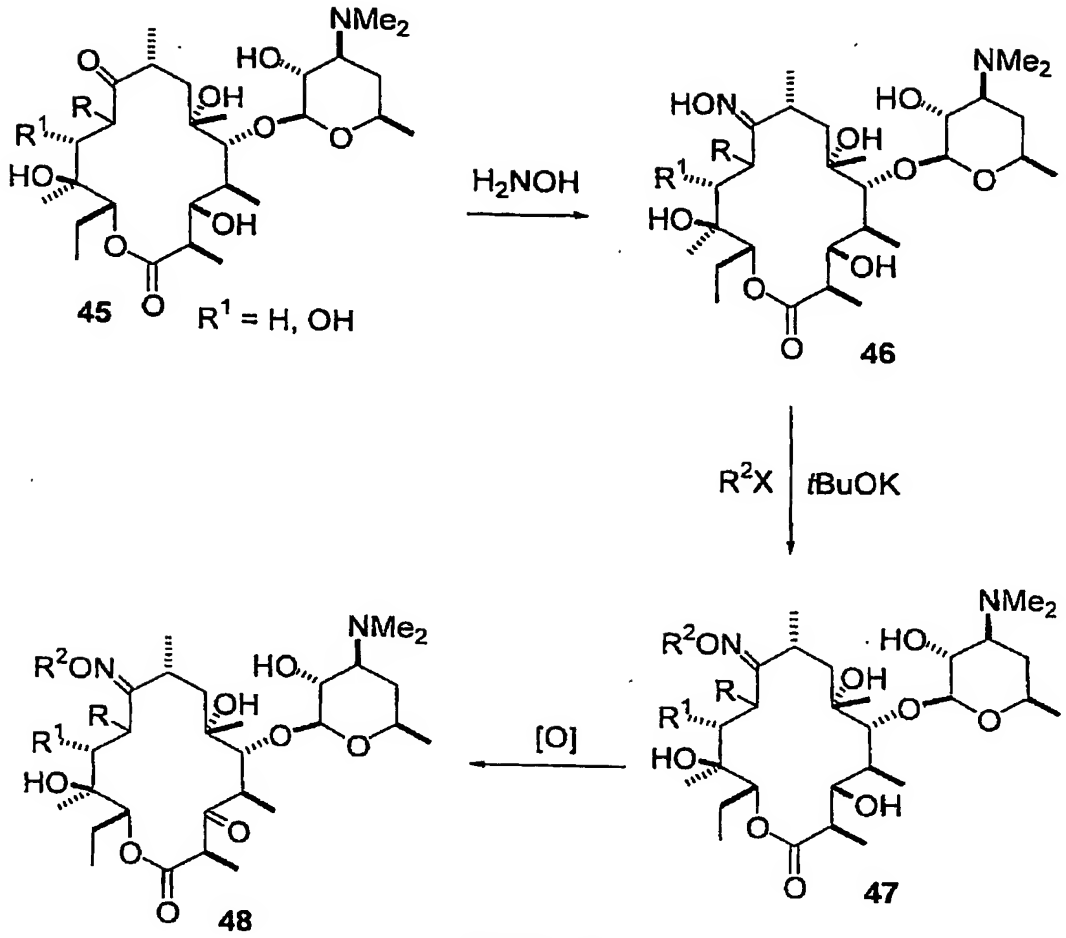
Scheme 9


NMe2
HO
R
O
OH
32
(i) TMS-triflate
Et3N, THF
(ii) R'2BH
TMSO
R'2B
OTMS
33
(i) H2O2
NaOH, EtOH
(ii) PPh3
HO
HO
38
R = Me 30%
R' = H
37
(i) Ac2O,NEt3
THF
(ii) NCS, Me2S
NEt3, CH2Cl2
(iii) MeOH.
39

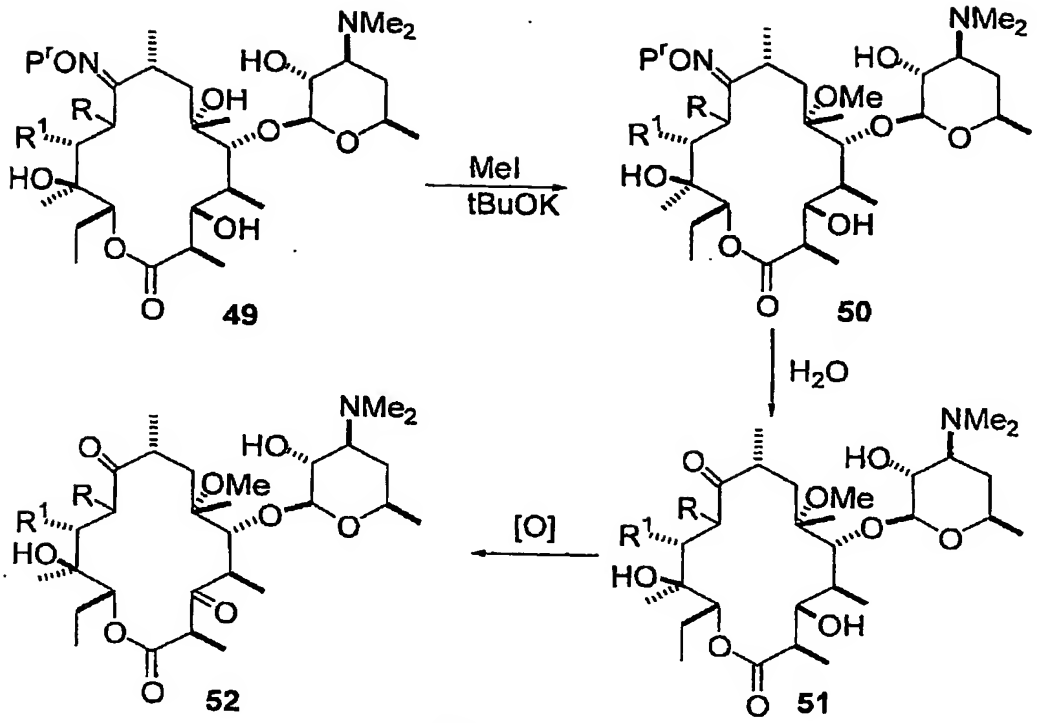
Scheme 10


NMe2
HO
R
O
OH
32
mCPBA
CH2Cl2
rt, 4 h
40
R = Me 49%
PPh3
THF
reflux
Pd(PPh3)4
dppe
toluene
reflux
41
R = Me 58%
42
M-H
43
[O]
44

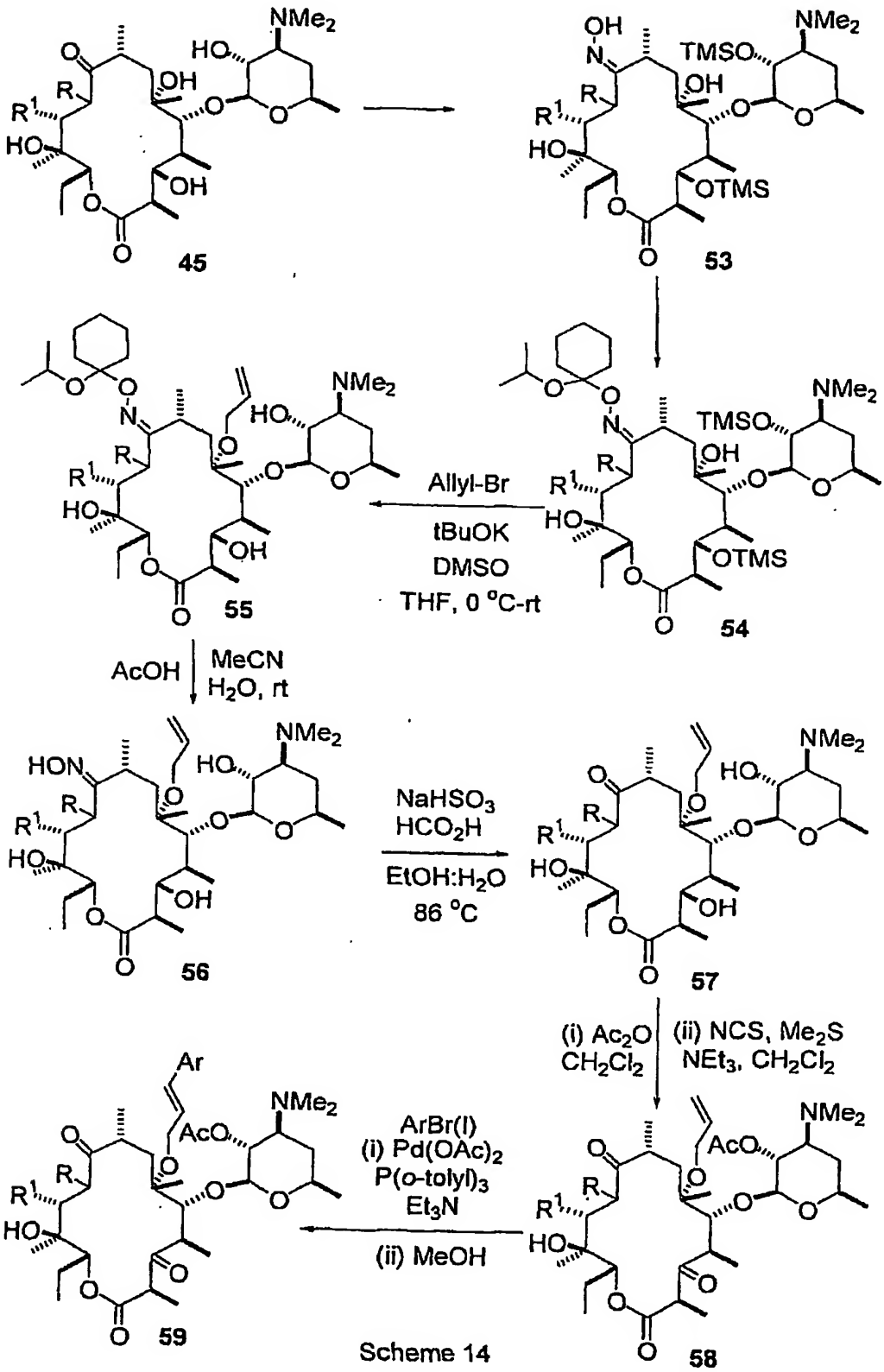
Scheme 11


NMe2
HO
O
R
OH
R1
HO
O
O
OH
O
O
45
R1 = H, OH
H2NOH
HON
NMe2
HO
R
OH
R1
HO
O
O
OH
O
46
R2X
tBuOK
R2ON
NMe2
HO
R
OH
R1
HO
O
O
OH
O
47
[O]
R2ON
NMe2
HO
R
OH
R1
HO
O
O
O
48

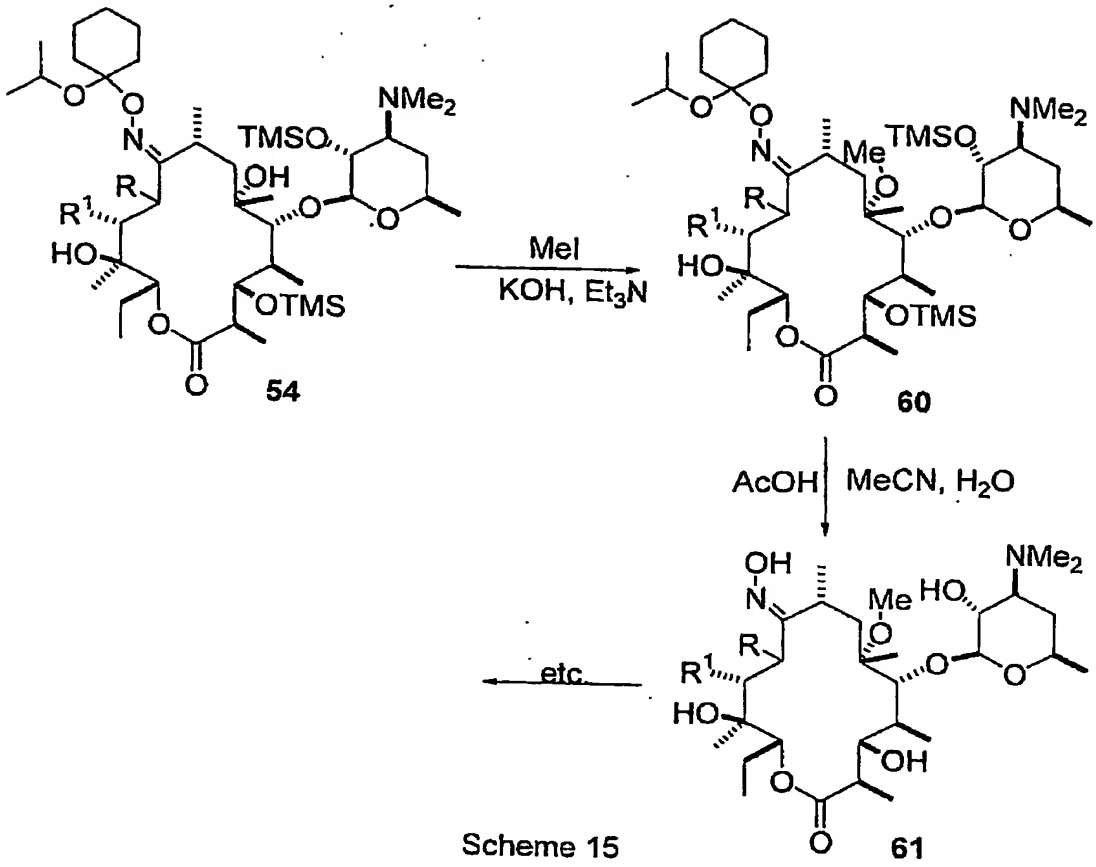
Scheme 12



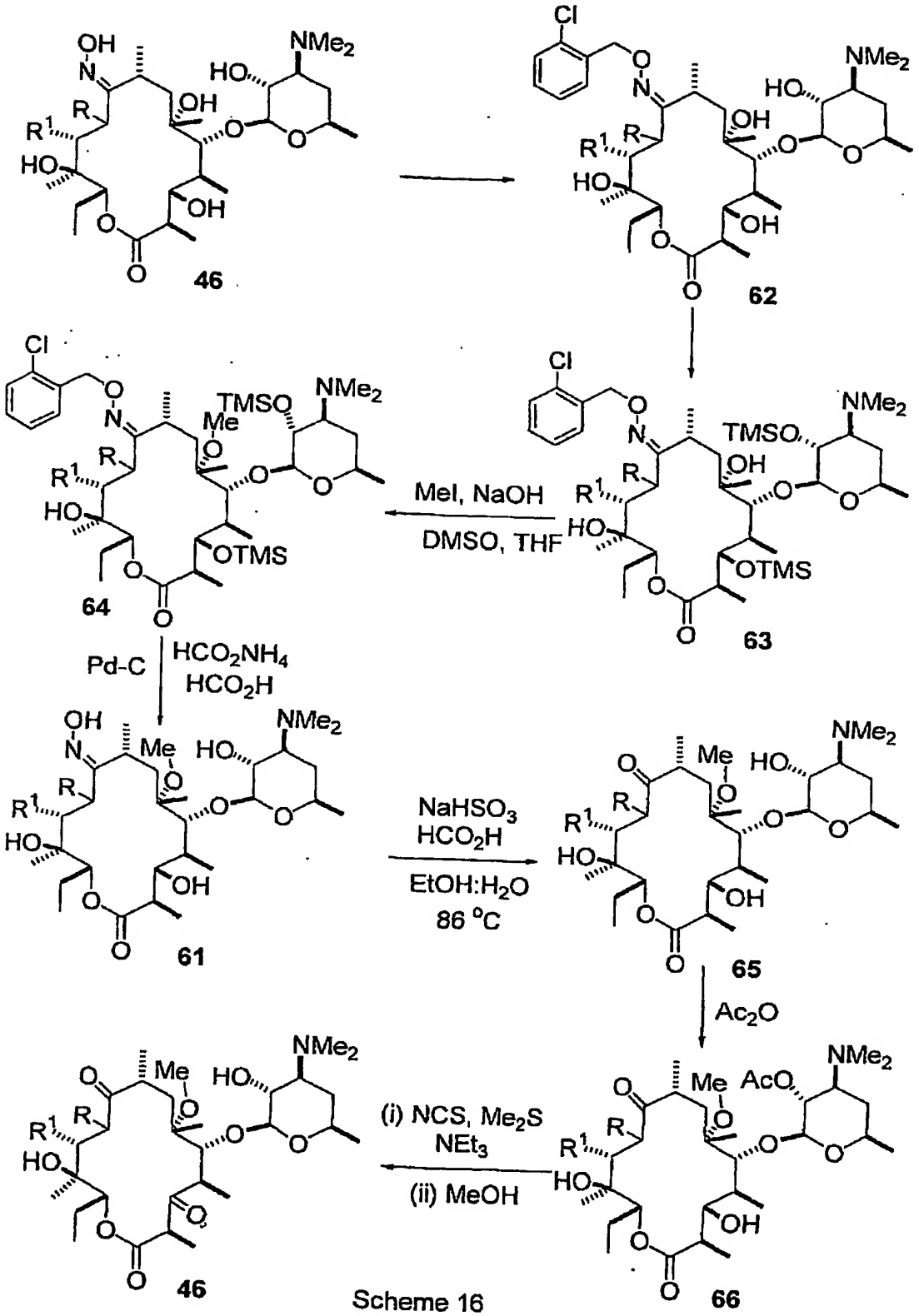
Scheme 13


45
53
54
55
Allyl-Br
tBuOK
DMSO
THF, 0 °C-rt
AcOH
MeCN
H2O, rt
56
NaHSO3
HCO2H
EtOH:H2O
86 °C
57
(i) Ac2O
CH2Cl2
(ii) NCS, Me2S
NEt3, CH2Cl2
58
ArBr(I)
(i) Pd(OAc)2
P(o-tolyl)3
Et3N
(ii) MeOH
59

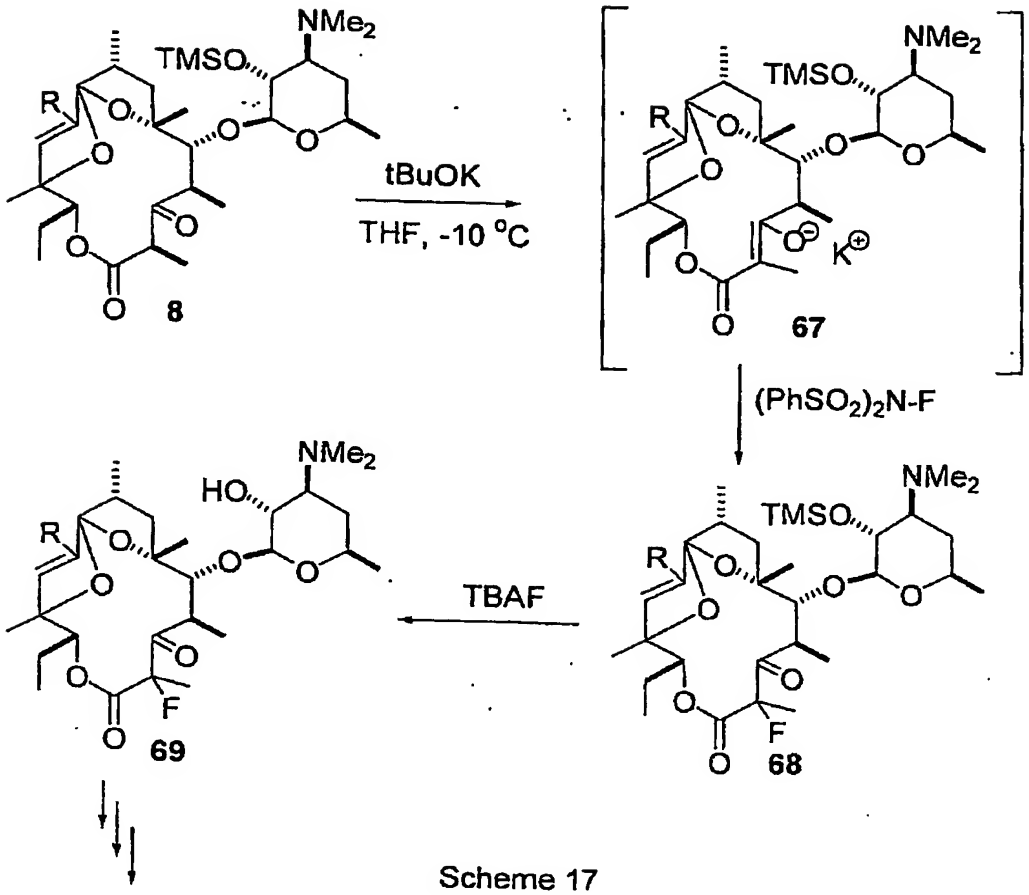
Scheme 14


NMe2
TMSO
OH
R
R1
HO
OTMS
O
54
MeI
KOH, Et3N
Me
60
AcOH
MeCN, H2O
OH
HO
etc
61

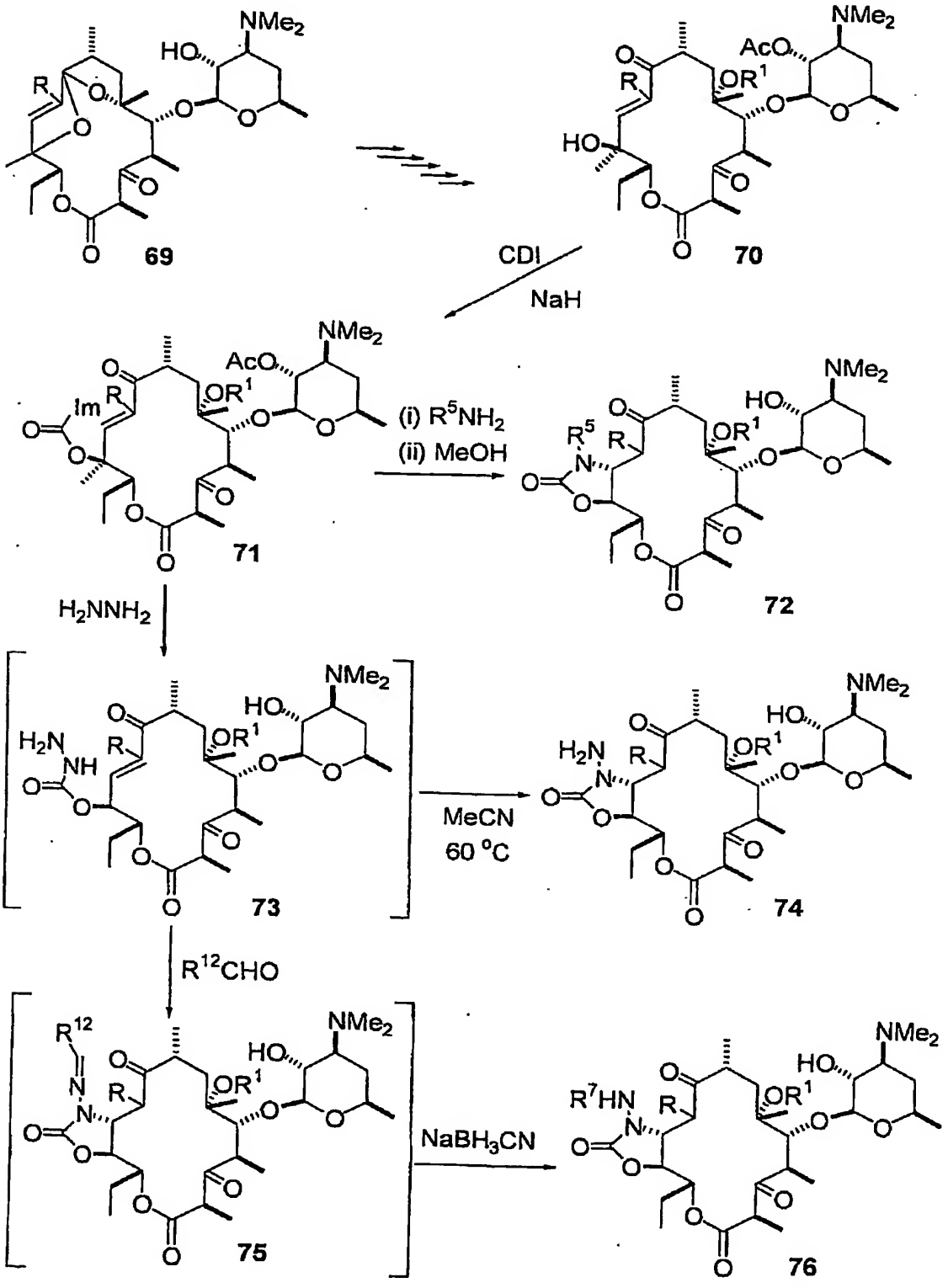
Scheme 15


46
62
63
64
61
65
66
MeI, NaOH
DMSO, THF
Pd-C
HCO_2NH_4
HCO_2H
$NaHSO_3$
HCO_2H
EtOH:H_2O
86 °C
Ac_2O
(i) NCS, Me_2S
NEt_3
(ii) MeOH

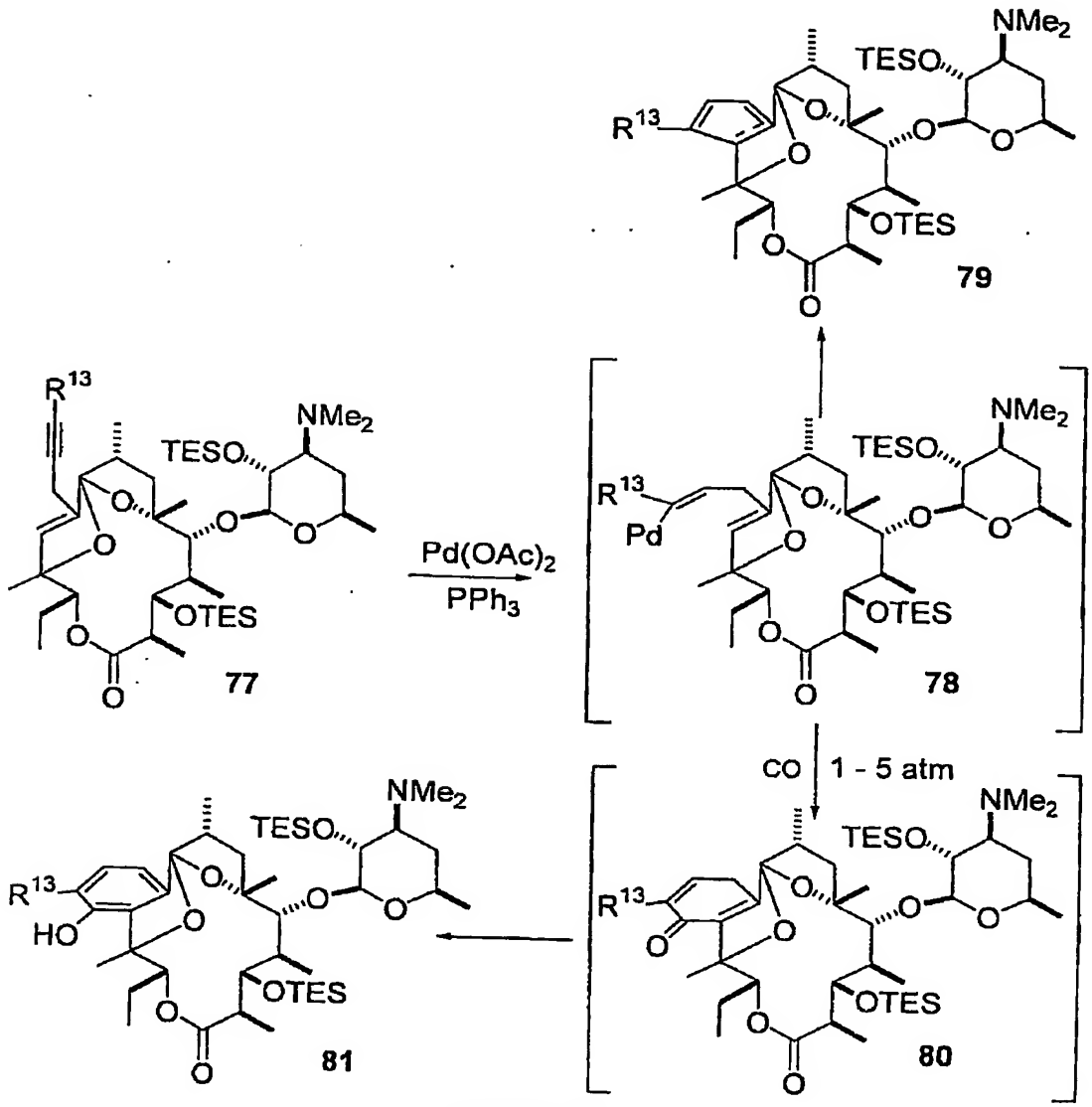
Scheme 16



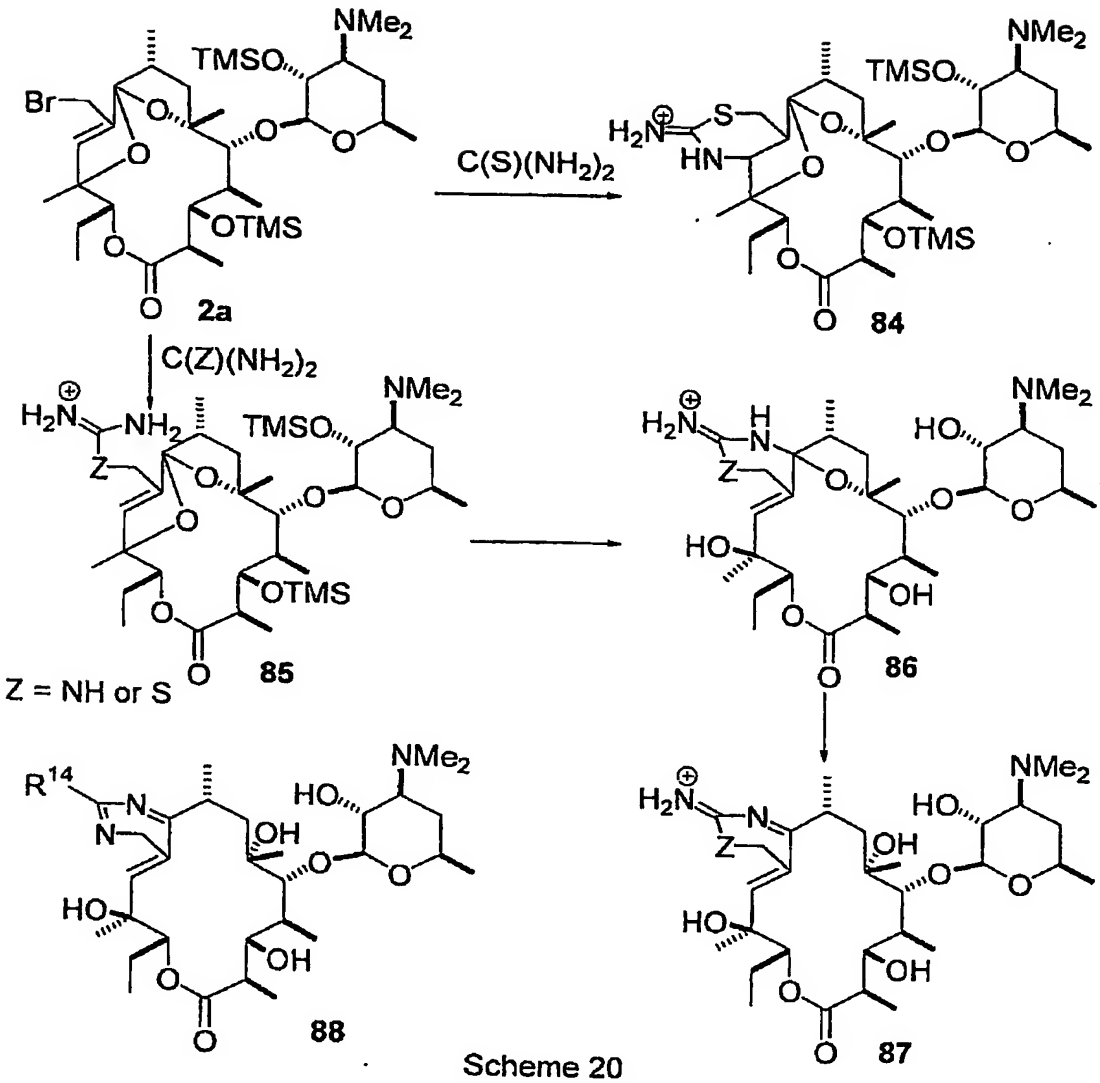
Scheme 17


NMe2
HO
R
O
O
O
O
O
69
CDI
NaH
AcO
OR1
HO
70
Im
(i) R5NH2
(ii) MeOH
R5
N
71
72
H2NNH2
H2N
NH
73
MeCN
60 °C
74
R12CHO
R12
N
75
NaBH3CN
R7HN
76

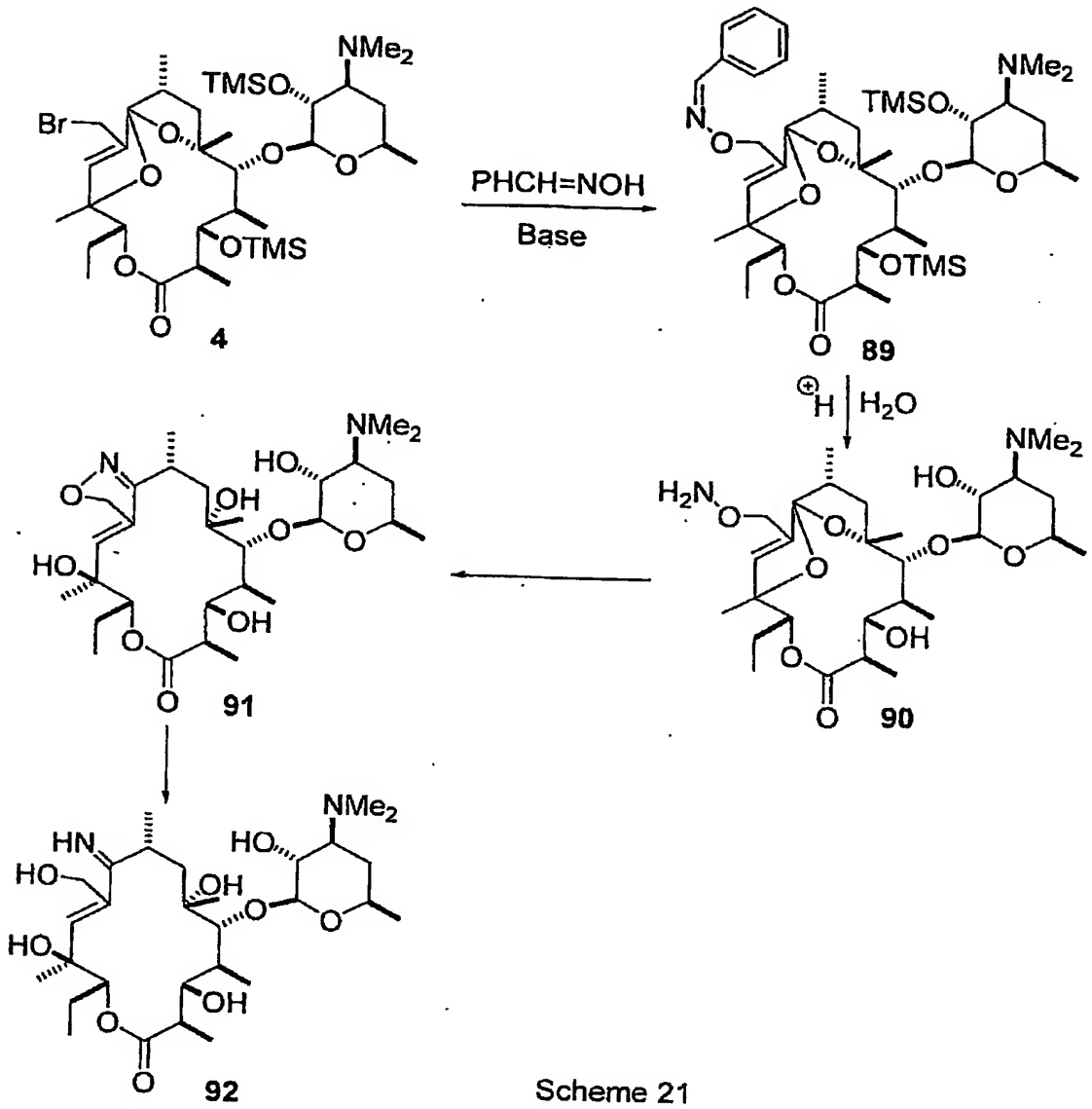
Scheme 18


NMe2
TESO
R13
OTES
79
R13
NMe2
TESO
77
Pd(OAc)2
PPh3
R13
Pd
78
CO
1 - 5 atm
NMe2
TESO
R13
HO
OTES
81
R13
80

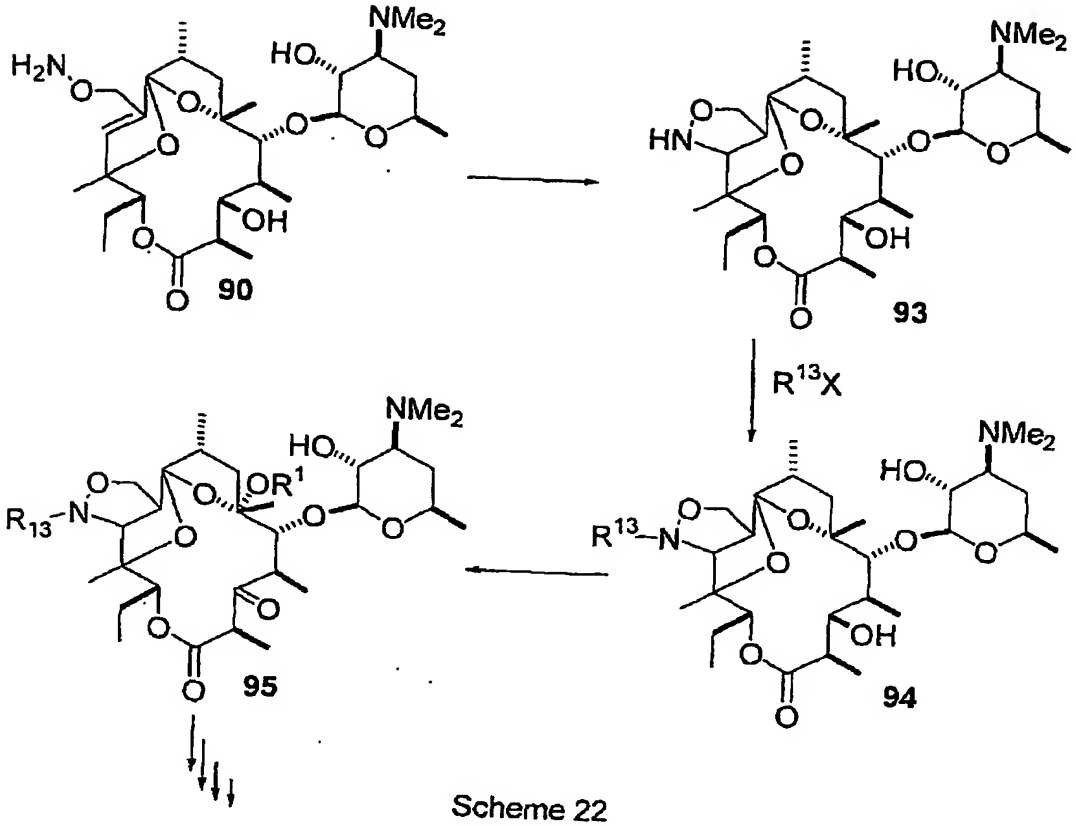
Scheme 19


NMe2
TMSO
Br
OTMS
2a
C(S)(NH2)2
84
C(Z)(NH2)2
85
Z = NH or S
86
87
88
R14
HO
OH

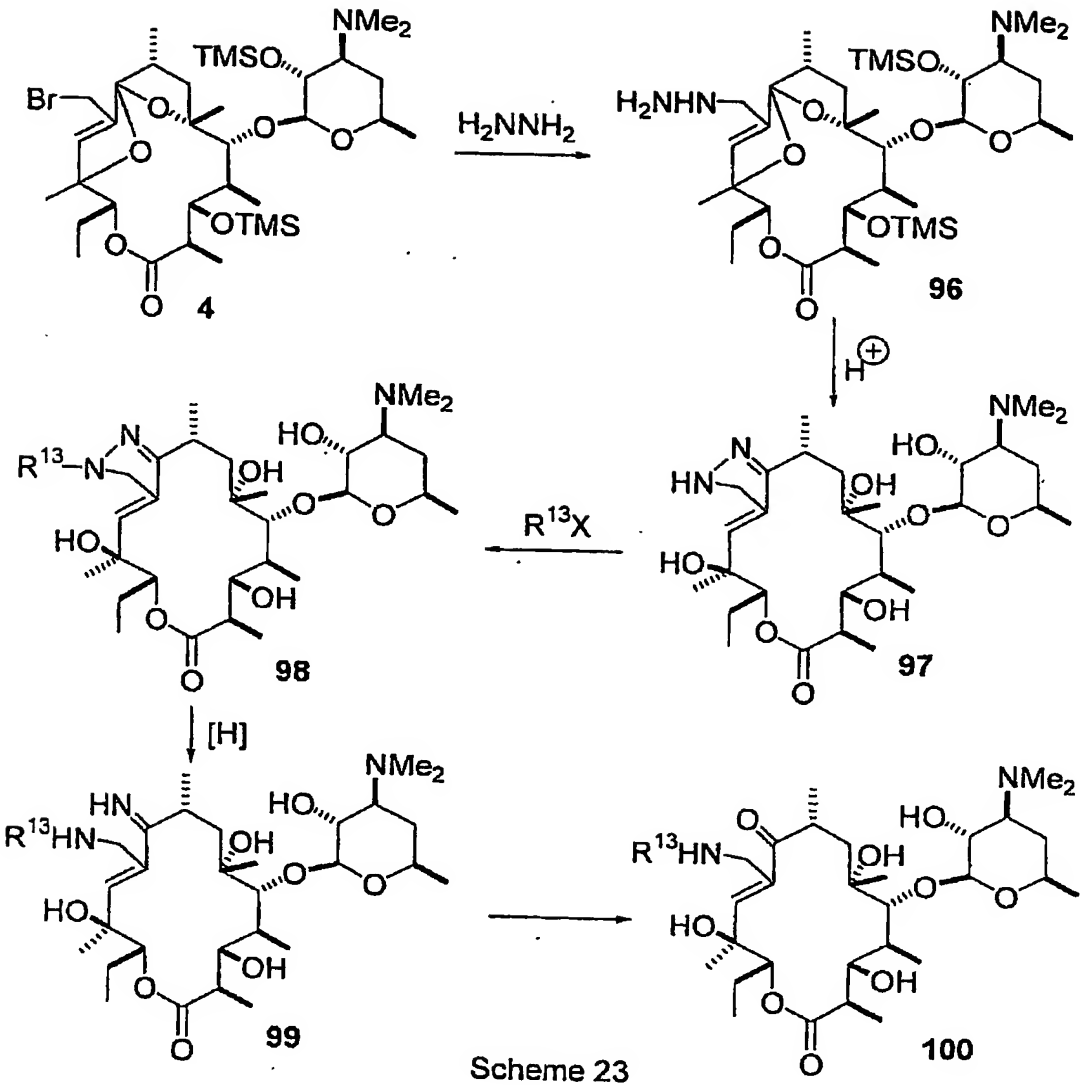
Scheme 20



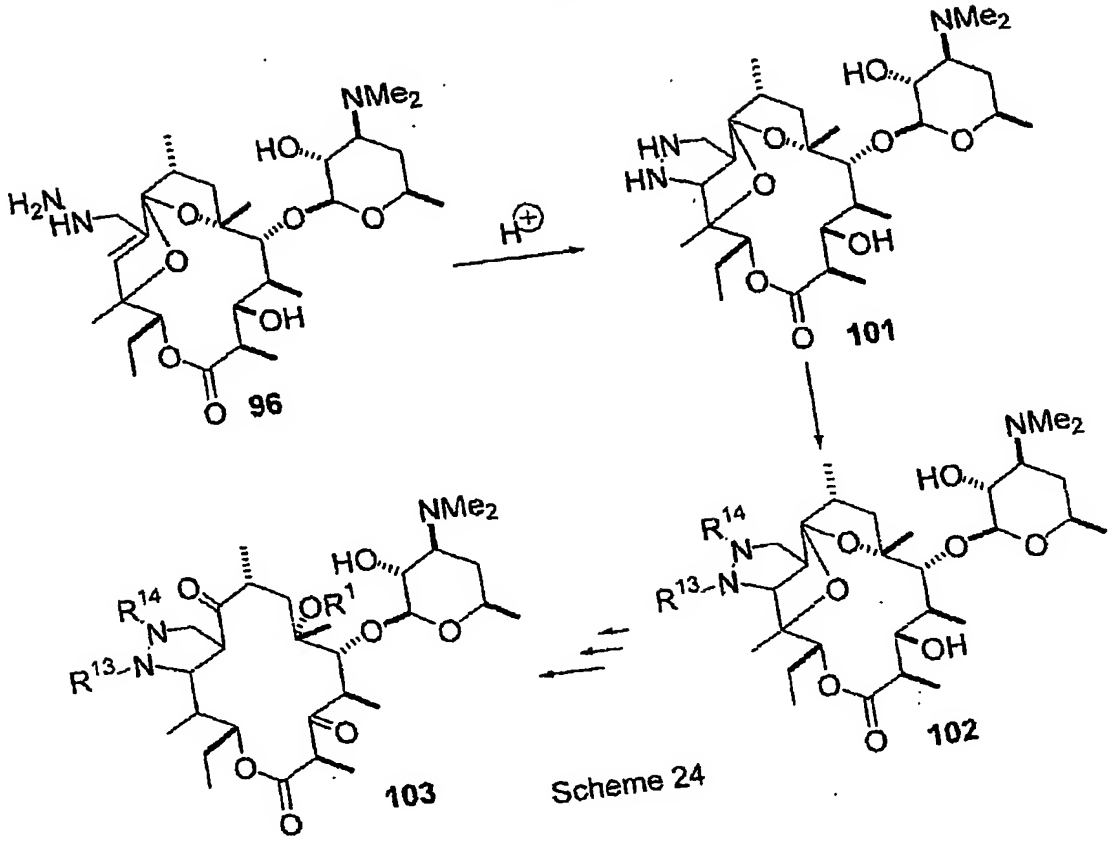
Scheme 21



Scheme 22


NMe2
TMSO
Br
O
O
O
O
OTMS
O
4
H2NNH2
H2NHN
96
H⊕
R13–N
N
HO
OH
HO
OH
98
R13X
HN
97
[H]
R13HN
99
100

Scheme 23



Scheme 24

EXPERIMENTAL

Erythralosamine (2). [Flynn, E. H.; Sigal, M. V.; Wiley, P. F.; Gerzon, K.; *J. Am. Chem. Soc.* **1954**, *76*, 3121-3131].

A solution of erythromycin A (6.66 g, 9.1 mmol) in a mixture of EtOH (60 mL) and 10 % HCl (200 mL) was stirred at ambient temperature for 24 h. The mixture was diluted with ethyl acetate (3 × 200 ml), washed with water (3 × 200 ml), dried ($MgSO_4$) and the solvent was evaporated. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:aq.NH_3 , initially in ratio 90:4:1, then in ratio 90:8:2. R_f 0.19. The product was a white crystalline solid; yield 3.22 g (66%), mp 208 °C.

HRMS: M 539.3412. Calc. for $C_{29}H_{49}NO$: 539.3458. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (t, 3 H, *J* 7.3 Hz, 13-CH_2CH_3), 0.93 (d, 3 H, *J* 7.0 Hz, 8-CH_3), 1.04 (d, 3 H, *J* 7.3 Hz, 4-CH_3), 1.10 (d, 3 H, *J* 7.4 Hz, 2-CH_3), 1.10 – 1.12 (m, 1 H, CHH-4'), 1.17 (d, 3 H, *J* 6.1 Hz, 5'-CH_3); 1.23 (s, 3 H, 12-CH_3), 1.29 – 1.36 (m, 1 H, 13-$CHHCH_3$), 1.40 (s, 3 H, 6-CH_3), 1.58 (dd, 1 H, *J* 13, 6.4 Hz, 7-CHH), 1.59-1.64 (m, 2 H, 13-$CHHCH_3$; CHH-4'), 1.85 (d, 3 H, *J* 1.3 Hz, 10-CH_3), 2.23 – 2.26 (m, 1 H, H-4), 2.26 (s, 6 H, $N(CH_3)_2$), 2.29 – 2.34 (pseudo t, 1 H, *J* 13 Hz, 7-CHH), 2.44 – 2.45 (m, 1 H, H-3'), 2.44 – 2.47 (m, 1 H, H-8), 2.71 – 2.74 (m, 1 H, 2-H), 3.19 (dd, 1 H, *J* 10.1, 7.3 Hz, H-2'), 3.40 (d, 1 H, *J* 8.2 Hz, H-5), 3.44 – 3.46 (m, 1 H, H-5'), 4.16 (d. 1 H, *J* 7.3 Hz, H-1'), 4.25 (m, 1 H, H-3), 4.96 (dd, 1 H, *J* 11.5, 2.8 Hz, H-13), 5.29 (d, 1 H, *J* 1.4 Hz, H-11). ^{13}C NMR ($CDCl_3$): δ 10.3 (13-CH_2CH_3), 12.0 (8-Me), 12.6 (4-Me), 13.7 (2-Me), 14.0 (10-Me), 21.2 (5'-Me), 23.1 (12-Me), 24.4 (C-14), 28.9 (C-4'), 29.6 (6-Me), 40.1 (C-8), 40.4 (N-Me_2), 42.9 (C-7), 44.5 (C-4), 46.8 (C-2), 65.5 (C-3'), 69.4 (C-5'), 70.1 (C-2'), 71.2 (C-3), 78.9 (C-13), 82.1 (C-6), 87.1 (C-5), 88.8 (C-12), 104.5 (C-1'), 120.0 (C-9), 128.5 (C-11), 139.2 (C-10), 178.5 (C-1). IR (ATR plate) (CH_2Cl_2) ν = 3461 (m), 2971 (s), 2933 (s), 2860 (s), 1727 (s), 1456 (s), 1381 (m), 1373 (m), 1323 (w), 1277 (w), 1171 (s), 1112 (s), 1098 (s), 1073 (s), 1023 (m), 991 (m), 905 (w.). MS(EI): 539 (M^+, 13%), 174 (11), 163 (10), 159 (14), 158 (100), 149 (19), 137 (29), 136 (22), 123 (43), 116 (16), 98 (21), 72 (11).

$O^{2',3}$-Bis(trimethylsilyl) erythralosamine (2a).

A solution of erythralosamine (2) (1.59 g, 0.0029 mol) and triethylamine (2.4 ml, 0.0174 mol) in THF (40 ml) under argon was cooled to –78 °C and trimethylsilyl trifluoromethanesulfonate (1.59 ml, 0.0088 mol) added dropwise. The mixture was stirred for 20 h, extracted into ethyl

acetate, the solution shaken with brine, dried ($MgSO_4$) and evaporated. The residual material was subjected to flash chromatography on silica gel using hexane:Et_2O 3:1 with 1% Et_3; yield: 1.59 g (80%) of a crystalline material.

HRMS: M 684.4338. Calc. for $C_{35}H_{65}NO_8Si_2$: 684.4321. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.09/0.13 (2 × s, 2 × 9H, 3/2' $Si(CH_3)_3$), 0.83 (t, 3 H, *J* 7.4 Hz, 13-CH_2CH_3), 0.91 (d, 3 H, *J* 7.5 Hz, 4-CH_3), 0.93 (d, 3 H, *J* 7.4 Hz, 8-CH_3), 1.02 (d, 3 H, *J* 7.4 Hz, 2-CH_3), 1.15 (d, 3 H, *J* 6.0 Hz, 5'-CH_3), 1.17 – 1.22 (m, 1 H, CHH-4'), 1.23 (s, 3 H, 12-CH_3), 1.29 – 1.35 (m, 1 H, 13-CHHCH$_3$), 1.46 (s, 3 H, 6-CH_3), 1.57 – 1.66 (m, 3 H, CHH-7/13-CHHCH$_3$/HH-4'), 1.79 (d, 3 H, *J* 1.1 Hz, 10-CH_3), 2.14 – 2.28 (m, 2 H, H-4/CHH-7), 2.24 (s, 6 H, $N(CH_3)_2$), 2.42 – 2.53 (m, 3 H, H-8/H-3'/H-2), 3.19 (dd, 1 H, *J* 9.5, 7.5 Hz, H-2'), 3.28 (d, 1 H, *J* 11.0 Hz, H-5), 3.37 – 3.40 (m, 1 H, H-5'), 4.05 (d. 1 H, *J* 7.1 Hz, H-1'), 4.15 (d, 1 H, *J* 6.1 Hz, H-3), 5.00 (dd, 1 H, *J* 11.7, 3.0 Hz, H-13), 5.49 (d, 1 H, *J* 1.0 Hz, H-11). ^{13}C NMR ($CDCl_3$): δ 0.7/0.7 (2 × $Si(CH_3)_3$, 10.3 (13-CH_2CH_3), 11.1 (4-Me), 12.1 (8-Me), 13.9 (10-Me), 16.0 (2-Me), 21.2 (5'-Me), 23.3 (12-Me), 24.3 (13-CH_2CH_3), 29.7 (C-4'), 31.0 (6-Me), 40.1 (C-8), 41.0 (NMe_2), 43.0 (C-7), 46.6 (C-4), 48.7 (C-2), 65.8 (C-3'), 68.8 (C-5'), 71.2 (C-3), 72.3 (C-2'), 78.3 (C-13), 82.5 (C-6), 85.9 (C-5), 88.8 (C-12), 105.2 (C-1'), 119.9 (C-9), 128.4 (C-11), 138.8 (C-10), 178.0 (C-1). ν_{max}(film)cm^{-1} (CH_2Cl_2) 2971 (s), 2935 (s), 2877 (m), 1734 (s), 1456 (m), 1372 (m), 1249 (s), 1173 (s), 1099 (s), 1049 (s), 902 (s), 839 (s).

$O^{2',3}$-Bis(triethylsilyl)erythralosamine (2b).

A solution of erythralosamine (**2**) (0.673 g, 0.0012 mol)) and triethylamine (0.50 ml, 0.0036 mmol) in dichloromethane (10 ml) under argon was cooled to -78 °C and the TES-triflate (0.81 ml, 0.0036 mmol) added dropwise. Ethyl acetate was added after 24 h, the solution shaken brine and dried ($MgSO_4$) before evaporation to dryness. The residual material was subjected to flash chromatography on silica gel using hexane:Et_2O 3:1 and 1% Et_3N; yield 0.75 g (81%) of a white crystalline material.

HRMS: M, 768.5248. Calc. for $C_{41}H_{77}NO_8Si_2$: 768.5260. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.59/0.68 (q, 2 × 6 H, (J ??), 2 × $(CH_3)_3(CH_2)_3$ Si), 0.84 (t, 3 H, *J* 7.3 Hz, 13-CH_2CH_3), 0.90 – 0.94 (m, 15 H, 4-CH_3/ 8-CH_3/$(CH_3)_3(CH_2)_3$ Si), 1.06 (d, 3 H, *J* 7.3 Hz, 2-CH_3), 1.15 (d, 3 H, *J* 6.1 Hz, 5'-CH_3), 1.14 – 1.19 (m, 1 H, CHH-4'), 1.24 (s, 3 H, 12-CH_3), 1.26 – 1.35 (m, 1 H, 13-CHHCH$_3$), 1.46 (s, 3 H, 6-CH_3), 1.56 – 1.65 (m, 3 H, 7-CHH/CHH-14/CHH-4'), 1.77 (d, 3 H, *J* 1.1 Hz, 10-CH_3), 2.20 – 2.26 (m, 2 H, H-4/CHH-7), 2.20 (s, 6 H, $N(CH_3)_2$), 2.39 – 2.45

(m, 1 H, H-3'), 2.46 – 2.52 (m, 2 H, H-8/H-2), 3.19 (m, 1H, H-2'), 3.28 –3.30 (m, 1 H, H-5'), 3.29 (d, 1 H, *J* 11.0 Hz, H-5), 4.06 (d. 1 H, *J* 7.0 Hz, H-1'), 4.16 (d, 1 H, *J* 6.3 Hz, H-3), 5.00 (dd, 1 H, *J* 11.7, 2.6 Hz, H-13), 5.49 (d, 1 H, *J* 1.1 Hz, H-11). ^{13}C NMR (300 MHz, $CDCl_3$): δ 5.3/5.6 $(CH_3)_3(\underline{C}H_2)_3$ Si), 7.0/7.1 $(\underline{C}H_3)_3(CH_2)_3$ Si), 10.3 (13-$CH_2\underline{C}H_3$), 10.5 (4-Me), 12.25 (8-Me), 13.8 (10-Me), 16.0 (2-Me), 21.2 (5'-Me), 23.2 (12-Me), 24.3 (13-$\underline{C}H_2CH_3$), 29.2 (C-4'), 31.3 (6-Me), 40.2 (C-8), 41.0 (N-Me_2), 43.0 (C-7), 47.3 (C-4), 49.4 (C-2), 66.2 (C-3'), 68.7 (C-5'), 71.0 (C-3), 72.1 (C-2'), 78.3 (C-13), 82.7 (C-6), 85.3 (C-5), 88.8 (C-12), 105.9 (C-1'), 119.9 (C-9), 128.2 (C-11), 138.9 (C-10), 178.1 (C-1).

$O^{2',3}$-Bis(*t*-butyldimethylsilyl)erythralosamine (2c).

A solution of erythralosamine (**2**) (0.475 g, 0.880 mmol) and triethylamine (0.37 ml, 2.640 mmol) in CH_2Cl_2 (5 ml) was cooled to 0 °C and TBDMS-triflate (0.50 ml, 2.640 mmol) was added dropwise to the reaction mixture. Water was added to the cold reaction mixture after 22 h, the mixture extracted with ethyl acetate, the extracts shaken with aqueos sodium hydrogen carbonate, with brine, dried ($MgSO_4$) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using hexane:Et_2O 3:1; yield 0.593 g (89%) of a white crystalline solid, mp 92 – 93 °C.

HRMS: [M+1], 768.5297. Calc. for $C_{41}H_{77}NO_8Si_2$: 768.5260. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01/0.04/0.08/0.19 (4 × s, 4 × 3 H, 2 × $(CH_3)_3C(C\underline{H}_3)_2$ Si), 0.84 (t, 3 H, *J* 7.3 Hz, 13-$CH_2C\underline{H}_3$), 0.86/0.90 (2 × s, 2 × 9 H, 2 × $(C\underline{H}_3)_3C(CH_3)_2$ Si), 0.94 (d, 3 H, *J* 7.2 Hz, 8-CH_3), 0.96 (d, 3 H, *J* 7.5 Hz, 4-CH_3), 1.06 (d, 3 H, *J* 7.4 Hz, 2-CH_3), 1.14 (d, 3 H, *J* 6.0 Hz, 5'-CH_3), 1.14 – 1.21 (m, 1 H, CH<u>H</u>-4'), 1.23 (s, 3 H, 12-CH_3), 1.29 – 1.35 (m, 1 H, 13-CH<u>H</u>CH_3), 1.47 (s, 3 H, 6-CH_3), 1.56 – 1.66 (m, 3 H, CH<u>H</u>-7/13-C<u>H</u>HCH_3/CH<u>H</u>-4'), 1.75 (s, 3 H, 10-CH_3), 2.15 – 2.21 (m, 2 H, <u>H</u>-4/CH<u>H</u>-7), 2.17 (s, 6 H, N($C\underline{H}_3)_2$), 2.39 – 2.44 (m, 1 H, H-3'), 2.47 – 2.56 (m, 2 H, H-8/H-2), 3.13 (m, 1 H, H-2'), 3.36 (m, 1 H, H-5'), 3.44 (d, 1 H, *J* 11.3 Hz, H-5), 4.06 (d. 1 H, *J* 7.1 Hz, H-1'), 4.22 (d, 1 H, *J* 5.3 Hz, H-3), 4.96 (dd, 1 H, *J* 11.6, 2.5 Hz, H-13), 5.47 (d, 1 H, *J* 1.0 Hz, H-11). ^{13}C NMR (300 MHz, $CDCl_3$): δ -4.4/-4.3/-3.0 $(CH_3)_3C(\underline{C}H_3)_2Si$), 10.3 (13-$CH_2\underline{C}H_3$), 11.5 (4-Me), 12.4 (8-Me), 13.8 (10-Me), 16.4 (2-Me), 18.5/18.6 $(CH_3)_3\underline{C}(CH_3)_2Si$), 21.2 (5'-Me), 23.2 (12-Me), 24.2 (13-$\underline{C}H_2CH_3$), 26.1/26.3 $(\underline{C}H_3)_3C(CH_3)_2Si$), 29.4 (C-4'), 30.5 (6-Me), 40.5 (C-8), 41.2 (N-Me_2), 43.3 (C-7), 48.0 (C-4), 50.5 (C-2), 66.3 (C-3'), 68.8 (C-5'), 70.3 (C-3), 72.2 (C-2'), 78.2 (C-13), 83.3 (C-6), 84.7 (C-5), 89.0 (C-12), 104.9 (C-1'), 120.0 (C-9), 127.8 (C-11), 139.0 (C-10), 178.3 (C-1). IR (film))

(CH_2Cl_2) v = 2970 (s), 2933 (s), 2856 (m), 1736 (m), 1461 (m), 1454 (m), 1382 (w), 1371 (w), 1250 (w), 1173 (m), 1126 (m), 1098 (s), 1072 (m), 1042 (s), 1003 (w), 900 (w), 835 (s), 773 (m).

Erythralosamine *N*-Oxide (3).

30% Hydrogen peroxide (1 ml) was added to a solution of erythralosamine (2) (1.4 g, 2.52 mmol) in methanol (10 ml) and the reaction mixture stirred at ambient temperature for 7 h. Saturated aqueous sodium bisulfite was added slowly to the reaction mixture to remove excess hydrogen peroxide before extraction with chloroform. The dried ($MgSO_4$) chloroform solution was evaporated. The residual material was the title compound that was sufficiently pure for use in the subsequent reaction. The product was a white crystalline solid with mp 153 – 155 °C; yield 100%.

HRMS: [M+1] 556.3484. Calc. for $C_{29}H_{50}BrNO_9$: 556.3480. ^1H NMR ($CDCl_3$): δ 0.82 (t, 3 H, *J* 7.2 Hz, 13-$CH_2C\underline{H}_3$), 0.92 (d, 3 H, *J* 7.0 Hz, 8-CH_3), 1.04 (d, 3 H, *J* 7.2 Hz, 4-$C\underline{H}_3$), 1.10 (d, 3 H, *J* 7.4 Hz, 2-$C\underline{H}_3$), 1.22 (d, 3 H, *J* 6.2 Hz, 5'-CH_3), 1.23 (s, 3 H, 12-CH_3), 1.32 – 1.34 (m, 1 H, C$\underline{H}$H-4'; m, 1 H, 13-C$\underline{H}$HCH_3), 1.41 (s, 3 H, 6-CH_3), 1.55 (dd, 1 H, *J* 13, 6.4 Hz, C$\underline{H}$H-7), 1.57 – 1.62 (m, 1 H, 13-C$\underline{H}$HCH_3), 1.84 (d, 3 H, *J* 1.1 Hz, 10-CH_3), 1.90 – 1.93 (m, 1 H, CH$\underline{H}$-4'), 2.25 – 2.27 (m, 1 H, 4-H), 2.27 – 2.33 (pseudo t, 1 H, *J* 13 Hz, CH$\underline{H}$-7), 2.44 – 2.47 (m, 1 H, H-8), 2.65 – 2.68 (m, 1 H, 2-H), 3.16 (s, 3 H, NMe), 3.17 (s, 3 H, NMe), 3.34 – 3.38 (m, 1 H, H-3'), 3.39 (d, 1 H, *J* 8.2 Hz, H-C), 3.55 – 3.59 (m, 1 H, H-5'), 3.74 (dd, 1 H, *J* 9.8, 7.1 Hz, H-2'), 4.20 (m, 1 H, H-3), 4.26 (d. 1 H, *J* 7.1 Hz, H-1'), 4.95 (dd, 1 H, *J* 11.5, 2.8 Hz, H-13), 5.49 (d, 1 H, *J* 1.1 Hz, H-11). ^{13}C NMR ($CDCl_3$): δ 10.7 (13-$CH_2\underline{C}H_3$), 12.2 (4-Me), 12.4 (8-Me), 14.4 (10-Me), 14.5 (2-Me), 21.4 (5'-Me), 23.6 (12-Me), 24.8 (13-$\underline{C}H_2CH_3$), 30.5 (6-Me), 35.3 (C-4'), 40.5 (C-8), 43.4 (C-7), 45.1 (C-4), 47.4 (C-2), 52.8 (NMe), 59.6 (NMe), 68.0 (C-5'), 71.4 (C-3), 71.9 (C-2'), 76.9 (C-3'), 79.2 (C-13), 82.4 (C-6), 88.2 (C-5), 89.3 (C-12), 104.8 (C-1'), 120.3 (C-9), 129.0 (C-11), 139.5 (C-10), 178.9 (C-1). IR (film) (CH_2Cl_2) v = 3397 (m), 2973 (s), 2934 (s), 2877 (m), 1717 (s), 1456 (m), 1372 (m), 1171 (s), 1112(m), 1099 (m), 1076 (s), 1064 (s), 1019(s), 993 (s), 906 (m)

10-Bromomethyl-10-desmethylerythralosamine *N*-Oxide (4).

A solution of *N*-bromosuccinimide in acetic acid (15 ml) was added to a solution of erythralosamine *N*-oxide (3) (1.56 g, 2.5 mmol) in acetic acid (20 ml) and the resultant

solution stirred at room temperature for 3 h when TLC showed the reaction to be complete. Most of the acetic acid was removed ar reduced pressure and aqueous potassium hydroxide was added to the reaction mixture until pH 9-11. The product was extracted into chloroform that was washed and dried ($MgSO_4$) before the solvent was distilled off. The product was isolated after flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3, initially in ratio 9:1: 0.1 and then 9:2:0.1; yield 0.95 g (60%) of a white crystalline material, mp 149 – 151 °C. (Found: C, 52.85; H, 7.19. $C_{29}H_{49}BrNO_9$ requires: C, 54.89; H, 7.62%)
HRMS: M, 634.2556. Calc. for $C_{29}H_{49}BrNO_9$: 634.2591; M 636.2550. Calc. for $C_{29}H_{49}BrNO_9$. 636.2570. ^{1}H NMR ($CDCl_3$): δ 0.84 (t, 3 H, *J* 7.2 Hz, 13-$CH_2C\underline{H}_3$), 0.94 (d, 3 H, *J* 7.2 Hz, 8-CH_3), 1.09 (d, 3 H, *J* 7.5 Hz, 4-CH_3), 1.12 (d, 3 H, *J* 7.5 Hz, 2-CH_3), 1.25 (d, 3 H, *J* 6.1 Hz, 5'-CH_3), 1.27 (s, 3 H, 12-CH_3), 1.32 – 1.36 (m, 1 H, C$\underline{H}$H-4; m, 1 H, 13-CH$\underline{H}CH_3$), 1.39 (s, 3 H, 6-CH_3), 1.59 (dd, 1 H, *J* 12.6, 6.7 Hz, CH$\underline{H}$-7), 1.61 – 1.67 (m, 1 H, 13-CH$\underline{H}CH_3$), 1.95 – 1.98 (m, 1 H, 4'-CH$\underline{H}$), 2.19 – 2.24 (m, 2 H, H-4; CH$\underline{H}$-7), 2.47 – 2.50 (m, 1 H, H-8), 3.06 – 3.08 (m, 1 H, H-2), 3.18 (s, 3 H, NMe), 3.21 (s, 3 H, NMe), 3.39 – 3.43 (m, 1 H, H- 3'), 3.46 (d, 1 H, *J* 4.2 Hz, 5-H), 3.57 – 3.60 (m, 1 H, H-5'), 3.72 (dd, 1 H, *J* 9.9, 7.2 Hz, H-2'), 4.00 (dd, 1H, *J* 13.8, 1.6 Hz, H-10), 4.33 (d. 1 H, *J* 7.1 Hz, H-1'), 4.37 (dd, 1H, *J* 7.9, 2.9, H-3), 4.59 (dd, 1 H, *J* 13.7, 1.7. H-10), 4.92 (dd, 1 H, *J* 11.3, 2.9 Hz, H-13), 6.09 (s, 1 H, H-11). ^{13}C NMR ($CDCl_3$): δ 10.2 (13-$CH_2\underline{C}H_3$), 12.4 (4-Me), 12.5 (8-Me), 16.5 (2-Me), 21.0 (5'-Me), 22.4 (12-Me), 24.4 (13-$\underline{C}H_2CH_3$), 27.1 (6-Me), 27.3 (C-10), 34.8 (C-4'), 39.9 (C-8), 42.7 (C-7), 42.9 (C-4), 45.4 (C-2), 52.6 (NMe), 58.9 (NMe), 67.9 (C-5'), 71.0 (C-2'), 71.9 (C-3), 76.4 (C-3'), 70.0 (C-13), 82.1 (C-6), 88.7 (C-5), 89.6 (C-12), 102.9 (C-1'), 119.7 (C-9), 134.0 (C-11), 140.0 (C-10), 179.9 (C-1). IR (film)) (CH_2Cl_2) ν = 3409 (m), 2973 (s), 2934 (s), 2877 (m), 1721 (s), 1456 (m), 1374 (m), 1169 (s), 1099 (m), 1060 (s), 1027 (m), 995 (m), 907 (w).

10-Bromomethyl-10-desmethylerythralosamine (5).

A solution of 10-bromomethyl-10-desmethylerythralosamine *N*-oxide (4) (2.60 g, 0.004 mol) and triphenylphosphine (2.20 g, 0.008 mol) in THF (30 ml) was heated under reflux for 17 h when TLC monitoring showed that the reaction had gone to completion. Most of the THF was removed by distillation, the residual material extracted into ethyl acetate, the extracts shaken with aqueous sodium bicarbonate, washed with brine, dried ($MgSO_4$), the solution evaporated and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 90:8:2; yield 2.13 g (86%) of a white crystalline material, mp 88 – 90 °C.

HRMS: M, 618.2607. Calc. for $C_{29}H_{48}BrNO_8$: 618.2636; M 620.2593. Calc. for $C_{29}H_{48}BrNO_8$: 620.2615. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3 H, *J* 7.3 Hz, 13-$CH_2C\underline{H}_3$), 0.93 (d, 3 H, *J* 7.1 Hz, 8-CH_3), 1.09 (d, 3 H, *J* 7.5 Hz, 2-CH_3), 1.12 (d, 3 H, *J* 7.5 Hz, 4-CH_3), 1.17 – 1.22 (m, 1 H, C<u>H</u>H-4'), 1.19 (d, 3 H, *J* 6.1 Hz, 5'-CH_3), 1.28 (s, 3 H, 12-CH_3), 1.31 – 1.36 (m, 1 H, 13-C<u>H</u>HCH$_3$), 1.38 (s, 3 H, 6-CH_3), 1.59 (dd, 1 H, *J* 12.7, 6.6 Hz, C<u>H</u>H-7), 1.62 – 1.69 (m, 1 H, CH<u>H</u>-4'), 1.62 – 1.69 (m, 1 H, 13-CH<u>H</u>CH$_3$), 2.13 – 2.19 (m, 1 H, 4-H), 2.21 – 2.25 (m, 1 H, CH<u>H</u>-7), 2.30 (s, 6 H, N(C<u>H</u>$_3$)$_2$), 2.45 – 2.52 (m, 1 H, *J* 13 Hz, H-8) , 2.45 – 2.52 (m, 1 H, H-3'), 3.08 (dq, 1 H, *J* 7.4, 2.6 Hz, H-2), 3.23 (dd, 1 H, *J* 10.0, 7.6 Hz, H-2'), 3.45 – 3.49 (m, 1 H, H-5'), 3.48 (d, 1 H, *J* 6.4 Hz, H-5), 4.00 (d, 1 H, *J* 14.0 Hz, H-10), 4.23 (d. 1 H, *J* 7.4 Hz, H-1'), 4.39 – 4.41 (m, 1 H, H-3), 4.57 (d, 1 H, *J* 14.0 Hz, H-10), 4.92 (dd, 1 H, *J* 11.3, 2.7 Hz, H-13), 6.03 (s, 1 H, H-11). ^{13}C NMR ($CDCl_3$): δ 10.3 (13-$CH_2\underline{C}H_3$), 12.2 (4-Me), 12.5 (8-Me), 16.6 (2-Me), 21.3 (5-Me), 22.4 (12-Me), 24.5 (13-$\underline{C}H_2CH_3$), 27.1 (C-10), 27.2 (6-Me), 28.9 (C-4'), 39.9 (C-8), 40.4 (N-Me_2), 42.9 (C-7/ C-4), 45.3 (C-2), 65.4 (C-3'), 69.6 (C-5'), 69.7 (C-2'), 71.9 (C-3), 79.2 (C-13), 82.2 (C-6), 86.0 (C-5), 89.6 (C-12), 103.2 (C-1'), 119.7 (C-9), 134.0 (C-11), 140.2 (C-10), 179.7 (C-1). IR (film, CH_2Cl_2) v = 3467 (m), 2973 (s), 2936 (s), 2877 (m), 1720 (s), 1456 (s), 1380 (s), 1315 (w), 1277 (w), 1170 (s), 1099 (s), 1074 (s), 1049 (s), 1027(s), 993 (m), 907 (m).

10-Bromomethyl- $O^{2',3}$-Bis(*t*-butyldimethylsilyl)-10-desmethylerythralosamine (5a). A solution of 10-bromomethyl-10-desmethylerythralosamine (5) (0.250 g, 0.404 mmol) and trimethylamine (0.17 ml, 1.212 mmol) in CH_2Cl_2 (5 ml) was cooled to 0 °C and TBDMS-triflate (0.23 ml, 1.212 mmol) added dropwise to the reaction mixture. Water was added to the cold reaction mixture after 17 h, the mixture extracted with ethyl acetate, the extracts shaken with aqueous sodium hydrogen carbonate, with brine, dried ($MgSO_4$) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using hexane:Et_2O 5:1; yield 0.25 g (73%) of a white crystalline solid, mp 151 – 152 °C. HRMS: [M+1], 846.4329. Calc. for $C_{41}H_{76}NO_8Si_2Br$: 846.4365. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06/0.07/0.19 (2 × $(CH_3)_3C(C\underline{H}_3)_2$ Si), 0.85 (t, 3 H, *J* 7.5 Hz, 13-$CH_2C\underline{H}_3$), 0.89/0.90 (2 × s, 2 × 9 H, 2 × $(C\underline{H}_3)_3C(CH_3)_2$ Si), 0.96 (d, 3 H, *J* 7.0 Hz, 8-CH_3), 0.94 (d, 3 H, *J* 7.1 Hz, 4-CH_3), 1.06 (d, 3 H, *J* 7.5 Hz, 2-CH_3), 1.14 (d, 3 H, *J* 6.0 Hz, 5'-CH_3), 1.16 – 1.21 (m, 1 H, CH<u>H</u>-4'), 1.28 (s, 3 H, 12-CH_3), 1.30 – 1.41 (m, 1 H, 13-C<u>H</u>HCH$_3$), 1.47 (s, 3 H, 6-CH_3), 1.56 – 1.66 (m, 3 H, C<u>H</u>H-7/13-C<u>H</u>HCH$_3$/CH<u>H</u>-4'), 2.07 – 2.11 (m, 2 H, H-4/CH<u>H</u>-7),

2.18 (s, 6 H, $N(C\underline{H}_3)_2$), 2.39 – 2.44 (m, 1 H, H-3'), 2.50 – 2.57 (m, 2 H, H-8/H-2), 3.13 (m, 1H, H-2'), 3.36 – 3.39 (m, 1 H, H-5'), 3.42 (d, 1 H, *J* 11.2 Hz, H-5), 3.91 (dd, 2H, *J* 13.5 Hz, 10-C<u>H</u>HBr), 4.07 (d. 1 H, *J* 7.2 Hz, H-1'), 4.22 (d, 1 H, *J* 5.0 Hz, H-3), 4.97 (dd, 1 H, *J* 11.6, 2.4 Hz, H-13), 5.99 (s, 1 H, H-11). ^{13}C NMR (300 MHz, $CDCl_3$): δ -4.4/-4.3/-4.2/-3.0 $(CH_3)_3C(\underline{C}H_3)_2Si)$, 10.3 (13-$CH_2\underline{C}H_3$), 11.9 (4-Me), 13.0 (8-Me), 16.2 (2-Me), 18.5/18.6 $(CH_3)_3\underline{C}(CH_3)_2Si)$, 21.2 (5'-Me), 22.9 (12-Me), 24.1 (13-$\underline{C}H_2CH_3$), 25.7 (10-$\underline{C}H_2$), 26.0/26.2 $(\underline{C}H_3)_3C(CH_3)_2Si)$, 29.3 (C-4'), 30.0 (6-Me), 40.7 (C-8), 41.2 (N-Me_2), 43.6 (C-7), 48.3 (C-4), 50.6 (C-2), 66.2 (C-3'), 68.9 (C-5'), 70.0 (C-3), 72.1 (C-2'), 78.1 (C-13), 83.9 (C-6), 84.7 (C-5), 88.4 (C-12), 105.0 (C-1'), 119.4 (C-9), 133.8 (C-11), 139.6 (C-10), 178.4 (C-1). IR (film, CH_2Cl_2) v = 2969 (s), 2934 (s), 2882 (w), 2856 (m), 1736 (s), 1473 (w), 1461 (m), 1381 (w), 1373 (w), 1250 (w), 1172 (s), 1124 (m), 1098 (s), 1067 (m), 1048 (s), 1031 (m), 903 (w), 835 (s), 774(m).

$O^{2'}$-Acetylerythralosamine (6).

Acetic anhydride (0.88 mL, 9.30 mmol) and triethylamine (1.29 mL, 9.30 mmol) were added to a solution of erythralosamine (**2**). (2.50 g, 4.69 mmol) in CH_2Cl_2 (15 mL) and the reaction mixture stirred at room temperature for 2 h until TLC monitoring showed full conversion. The reaction mixture was diluted with ethyl acetate, the solution shaken with 5% Na_2CO_3 (aq), with brine, dried ($MgSO_4$) and evaporated. The residual material was subjected to flash chromatography using silica gel, 90:4:1 CH_2Cl_2:MeOH:NH_3 (aq); yield 2.30 g (84%) of a white solid, mp 153 – 154 °C.

HRMS: M 581.3554. Calc. for $C_{29}H_{49}NO_8$: 581.3564. ^1H NMR (500 MHz, $CDCl_3$): δ 0.82 (t, 3 H, *J* 7.1 Hz, 13-$CH_2C\underline{H}_3$), 0.91 – 0.93 (m, 6 H, 8-CH_3/4-CH_3), 1.08 (d, 3 H, *J* 7.3 Hz, 2-CH_3), 1.17 (d, 3 H, *J* 6.0 Hz, 5'-CH_3), 1.23 (s, 3 H, 12-CH_3), 1.31 – 1.35 (m, 2 H, C<u>H</u>H-4'/13-C<u>H</u>HCH$_3$), 1.38 (s, 3 H, 6-CH_3), 1.54 (dd, 1 H, *J* 12.0, 5.5 Hz, CH<u>H</u>-7), 1.57 – 1.65 (m, 1 H, 13-C<u>H</u>HCH$_3$), 1.67 – 1.69 (m, 1 H, CH<u>H</u>-4'), 1.76 (d, 3 H, *J* 1.0 Hz, 10-CH_3), 2.03 (s, 3 H, 2'-OCOCH$_3$), 2.14 – 2.18 (m, 1 H, H-4), 2.25 (s, 6 H, $N(CH_3)_2$), 2.35 – 2.40 (pseudo t, 1 H, *J* 12.1 Hz, CH<u>H</u>-7), 2.38 – 2.42 (m, 1 H, H-8), 2.52-2.57 (m, 1 H, H-2), 2.68 (dt, 1 H, *J* 11.0, 3.0 Hz, H-3'), 3.34 (d, 1 H, *J* 9.5 Hz, H-5), 3.40 – 3.47 (m, 1 H, H-5'), 4.18 (m, 1 H, H-3), 4.23 (d. 1 H, *J* 7.5 Hz, H-1'), 4.78 (dd, 1 H, *J* 10.5, 8.0 Hz, H-2'), 4.97 (dd, 1 H, *J* 11.5, 2.8 Hz, H-13), 5.48 (d, 1 H, *J* 1.5 Hz, 11-H). ^{13}C NMR 300 MHz ($CDCl_3$): δ 10.2 (13-$CH_2\underline{C}H_3$), 11.2 (8-Me), 11.8 (4-Me), 13.7 (2-Me), 14.27 (10-Me), 21.0 (2'-OCO$\underline{C}H_3$), 21.3 (5'-Me), 23.3 (12-

Me), 24.3 (13-$\underline{C}H_2CH_3$), 30.5 (6-Me), 31.0 (C-4'), 39.9 (C-8), 40.7 (N-Me_2), 42.7 (C-7), 44.9 (C-4), 46.8 (C-2), 65.1 (C-3'), 69.0 (C-5'), 70.7 (C-2'), 71.0 (C-3), 78.9 (C-13), 81.7 (C-6), 86.7 (C-5), 88.7 (C-12), 102.6 (C-1'), 119.9 (C-9), 128.5 (C-11), 139.3 (C-10), 169.7 (C-2'-O$\underline{C}OCH_3$), 177.9 (C-1). IR (ATR plate) (CH_2Cl_2) v = 3477 (m), 2971 (s), 2933 (s), 2877 (m), 1747 (s), 1731 (s), 1456 (m), 1372 (s), 1322 (w), 1236 (s), 1171 (s), 1098 (m), 1060 (s), 1022 (m), 991 (m), 906 (w).

$O^{2'}$-Acetylerythralosamine-3 ketolide (7).

Dimethyl sulfide (0.24 mL, 7.72 mmol) was added dropwise from a syringe over 5 min to a stirred solution of *N*-chlorosuccinimide (NCS) (0.363 g, 2.72 mmol) in dichloromethane (8 mL) at –10 °C under argon. The solution was stirred at this temperature for 10 min before a solution of **$O^{2'}$-acetylerythralosamine (6)**. (1.05g, 1.81 mmol) in dichloromethane (12 mL) was added dropwise over 20 min. The mixture was stirred for 30 min at –10 to –5 °C when triethylamine (0.28 mL, 1.99 mmol) was added over 5 min. The mixture was stirred for an additional 45 min at this temperature and then allowed to reach room temperature and the solvent removed at reduced pressure. The residual material was extracted into ethyl acetate, the solution shaken with 5% Na_2CO_3, with brine, dried ($MgSO_4$) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using NEt_3:acetone:hexane 1:25:75; yield 0.66 g (63 %) of a white solid, mp 235 °C. R_f 0.17. HRMS: M 580.3480. Calc. for $C_{31}H_{49}NO_9$: 580.3480. ^{1}H NMR (500 MHz) ($CDCl_3$): δ 0.83 (t, 3 H, *J* 7.0 Hz, 13-$CH_2C\underline{H}_3$), 0.93 (d, 3 H, *J* 8.0, 8-CH_3), 1.06 (d, 3H, *J* 7.0, 4-CH_3), 1.15 (s, 3 H, 6-CH_3), 1.17 (d, 3 H, *J* 6.2 Hz, 5'-CH_3), 1.22 (s, 3 H, 12-CH_3), 1.27 (d, 3 H, *J* 6.9 Hz, 2-CH_3), 1.30 – 1.38 (m, 2 H, C$H\underline{H}$-4'/13-C$H\underline{H}CH_3$), 1.55 (dd, 1 H, *J* 13.1, 6.7 Hz, C$H\underline{H}$-7), 1.59 – 1.62 (m, 1 H, 13-C$H\underline{H}CH_3$), 1.69 – 1.72 (m, 1 H, C$H\underline{H}$-4'), 1.75 (d, 3 H, *J* 1.2 Hz, 10-CH_3), 2.02 (s, 3 H, 2'-O$\underline{C}OCH_3$), 2.12 – 2.17 (pseudo t, 1 H, *J* 13.5 Hz, C$H\underline{H}$-7), 2.25 (s, 6 H, N($C\underline{H}_3$)$_2$), 2.44 – 2.49 (m, 1 H, H-8), 2.68 (dt, 1 H, *J* 12.0, 3.0 Hz, H-3'), 3.03 – 3.09 (m, 1 H, H-4), 3.42 – 3.48 (m, 1 H, H-5'), 3.62 (d, 1 H, *J* 10.0 Hz, H-5), 3.69 (q, 1 H, *J* 7.0, H-2), 4.23 (d. 1 H, *J* 8.0 Hz, H-1'), 4.80 (dd, 1 H, *J* 10.5, 8.0 Hz, H-2'), 4.91 (dd, 1 H, *J* 11.5, 2.5 Hz, H-13), 5.47 (d, 1 H, *J* 1.2 Hz, H-11). ^{13}C NMR 300 MHz ($CDCl_3$): δ 10.2 (13-$CH_2\underline{C}H_3$), 12.5 (8-Me), 13.0 (10-Me), 15.2 (4-Me), 17.0 (2-Me), 20.9 (5'-Me), 21.2 (2'-OCO$\underline{C}H_3$), 23.3 (12-Me), 25.0 (13-$\underline{C}H_2CH_3$), 28.1 (6-Me), 30.9 (C-4'), 40.7 (N-Me_2), 41.0 (C-8), 42.5 (C-7), 52.2 (C-2), 53.1 (C-4), 63.0 (C-3'), 69.1 (C-5'), 71.2 (C-2'), 79.2 (C-13), 83.3 (C-6), 86.9 (C-5),

88.8 (C-12), 103.5 (C-1'), 120.4 (C-9), 127.7 (C-11), 139.24 (C-10), 169.1 (C-1), 169.7 (2'-O<u>C</u>OCH$_3$), 208.6 (C-3). IR (ATR plate) (CH_2Cl_2) v = 2971 (s), 2933 (s), 2876 (m), 1747 (s), 1711 (m), 1456 (m), 1371 (s), 1322 8w), 1237 (s), 1175 (s), 1112 (m), 1098 (m), 1060 (s), 1020 (w), 988 (m), 906 (w)

Erythralosamine 3-ketolide (8).

O$^{2'}$-Acetylerythralosamine-3 ketolide (7) (0.50 g, 0.86 mmol) was dissolved in methanol (10 mL) and the reaction mixture stirred at room temperature for 16 h until TLC monitoring showed full conversion. The solvent was removed under reduced pressure and the residual material purified by flash chromatography on silica gel using NEt_3:acetone:hexane 1:25:75. R_f 0.15. Yield 0.37 g (80 %) of a white solid, mp 179 °C.

HRMS: M 538.3354. Calc. for $C_{29}H_{47}NO_8$: 538.3374. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (t, 3 H, *J* 7.5 Hz, 13-$CH_2C\underline{H}_3$), 0.93 (d, 3 H, *J* 7.1, 8-CH_3), 1.16 – 1.17 (m, 9 H, 4-CH_3/ 6-$C\underline{H}_3$/ 5'-$C\underline{H}_3$), 1.20 – 1.22 (m, 1 H, H-4'), 1.22 (s, 3 H, 12-$C\underline{H}_3$), 1.28 (d, 3 H, *J* 7.1 Hz, 2-$C\underline{H}_3$), 1.30 – 1.38 (m, 1 H, 13-CH<u>H</u>CH$_3$), 1.57 – 1.64 (m, 3 H, CH<u>H</u>-7/13-CH<u>H</u>CH$_3$/CH<u>H</u>-4'), 1.80 (d, 3 H, *J* 1.2 Hz, 10-CH_3), 2.07 – 2.12 (pseudo t, 1 H, *J* 13.7 Hz, CH<u>H</u>-7), 2.25 (s, 6 H, N($C\underline{H}_3$)$_2$), 2.42 – 2.53 (m, 2 H, H-3/H-8), 3.15 – 3.23 (m, 2 H, H-4-/H-2'), 3.42 – 3.47 (m, 1 H, H-5'), 3.66 – 3.71 (m, 2 H, H-5/H-2), 4.17 (d, 1 H, *J* 7.3 Hz, H-1'), 4.91 (dd, 1 H, *J* 11.5, 2.5 Hz, H-13), 5.49 (d, 1 H, *J* 1.4 Hz, H-11). ^{13}C NMR 300 MHz ($CDCl_3$): δ 10.24 (13-$CH_2\underline{C}H_3$), 12.7 (8-Me), 13.4 (10-Me), 15.5 (4-Me), 17.2 (2-Me), 21.2 (5'-Me), 23.2 (12-Me), 23.9 (C-14), 28.0 (6-Me), 28.4 (C-4'), 40.3 (NMe_2), 41.3 (C-8), 42.9 (C-7), 52.1 (C-2), 53.2 (C-4), 65.7 (C-3'), 69.5 (C-5'), 70.0 (C-2'), 79.2 (C-13), 83.7 (C-6), 87.7 (C-5), 88.9 (C-12), 105.9 (C-1'), 120.4 (C-9), 127.8 (C-11), 139.0 (C-10), 169.3 (C-1), 209.1 (C-3). IR (ATR plate) (CH_2Cl_2) v = 3461 (m), 2971 (s), 2934 (s), 2833 (m), 2786 (m), 1750 (s), 1709 (m), 1670 (w), 1456 (s), 1370 (m), 1348 (m), 1327 (m), 1305 (m), 1174 (s), 1097 (s), 1075 (s), 1051 (s), 1020 (s), 989 (s), 905 (m).

Erythralosamine 3-ketolide *N*-Oxide (9).

30% Hydrogen peroxide (1 ml) was added to a solution of erythralosamine 3-ketolide (8) (0.307 g, 0.507 mmol) in methanol (2 ml) and the reaction mixture stirred at ambient temperature for 4 h. Saturated aqueous sodium bisulfite was added slowly to the reaction mixture to remove excess hydrogen peroxide before extraction with ethyl acetate. The dried

($MgSO_4$) chloroform solution was evaporated. The residual material was the title compound, which was sufficiently pure for use in the subsequent reaction. The product was a white crystalline solid with mp 139 – 141 °C; yield 73%.

HRMS: [M +1] 554.3315. Calc. for $C_{29}H_{47}NO_9$: 554.3323. ^{1}H NMR (500 MHz) ($CDCl_3$): δ 0.83 (t, 3 H, *J* 7.2 Hz, 13-$CH_2C\underline{H}_3$), 0.93 (d, 3 H, *J* 7.0, 8-CH_3), 1.16 (s, 6-CH_3), 1.18 – 1.22 (m, 9 H, 4-CH_3/12-CH_3/5'-CH_3), 1.27 (d, 3 H, *J* 6.9 Hz, 2-CH_3), 1.32 – 1.36 (m, 2 H, H-4'/13-$CH\underline{H}CH_3$), 1.56 – 1.62 (m, 2 H, $CH\underline{H}$-7/13-$CH\underline{H}CH_3$), 1.80 (s, 3 H, 10-$C\underline{H}_3$), 1.92 – 1.94 (m, 1H, H-4'), 2.07 – 2.13 (pseudo t, 1 H, *J* 13.5 Hz, $CH\underline{H}$-7), 2.45 – 2.52 (m, 1 H, H-8), 3.17 (s, 6 H, $NO(C\underline{H}_3)_2$), 3.17 – 3.22 (m, 1 H, H-4), 3.35 – 3.37 (m, 1H, H-3'), 3.56 – 3.59 (m, 1 H, H-5'), 3.66 – 3.71 (m, 2 H, H-5/H-2), 3.79 (d, 1 H, *J* 9.9, 7.1 Hz, H-2'), 4.27 (d, 1 H, *J* 7.0 Hz, H-1'), 4.90 (dd, 1 H, *J* 11.5, 2.5 Hz, H-13), 5.49 (s, 1 H, H-11). ^{13}C NMR 300 MHz ($CDCl_3$): δ 10.2 (13-$CH_2\underline{C}H_3$), 12.7 (8-Me), 13.5 (10-Me), 15.4 (4-Me), 17.2 (2-Me), 20.9 (5'-Me), 23.2 (12-Me), 23.9 (C-14), 28.1 (6-Me), 34.8 (C-4'), 41.3 (C-8), 42.8 (C-7), 52.2 (C-4), 52.3 (N-Me), 53.1 (C-2), 59.2 (N-Me), 67.7 (C-5'), 71.6 (C-2'), 76.3 (C-3'), 79.1 (C-13), 83.5 (C-6), 88.3 (C-5), 89.0 (C-12), 105.5 (C-1'), 120.4 (C-9), 127.8 (C-11), 138.9 (C-10), 169.3 (C-1), 209.1 (C-3). IR (film) (CH_2Cl_2) ν = 3398 (m), 2972 (s), 2934 (m), 287 (w), 1745 (s), 1456 (m), 1370 (m), 1348 (w), 1322 (w), 1305 (w), 1175 (s), 1113 (m), 1098 (m), 1077 (s), 1064 (s), 1018 (m), 1006 (m), 990 (m), 906 (w)

10-Benzyl-10-desmethylerythralosamine (12).

A solution of 10-bromomethyl-10-desmethylerythralosamine (5) (0.280 g, 0.453 mmol) in NMP (5 mL) was degassed and tris(2-furyl)phosphine (0.025 g, 0.109 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.014 g, 0.014 mmol) added. The reaction mixture was heated 50 °C for 10 min before tributyl(phenyl)stannane (0.30 mL, 0.906 mmol) was added. The reaction mixture was heated at 100 °C for 20 h. The cold reaction mixture was extracted into ethyl acetate, the solution shaken with aqueus sodium hydrogen carbonate, with brine, dried ($MgSO_4$) and the solvents distilled off at reduced pressure. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 90:4:1 and then CH_2Cl_2:MeOH (9:2); yield 0.168 g (60%) of a white crystalline material mp. 151 – 152 °C

HRMS: M 616.3847. Calc. for $C_{35}H_{53}NO_8$: 616.3843. ^{1}H NMR ($CDCl_3$): δ 0.79 (t, 3 H, *J* 7.3 Hz, 13-$CH_2C\underline{H}_3$), 1.06 (d, 3 H, *J* 6.9 Hz, 8-CH_3), 1.08 – 1.11 (m, 1 H, $C\underline{H}$H-4'), 1.13 (d, 3 H, *J* 7.5 Hz, 4-CH_3), 1.15 (d, 3 H, *J* 8.2 Hz, 2-CH_3), 1.17 (d, 3 H, *J* 6.5 Hz, 5'-CH_3), 1.15 – 1.18

(m, 1 H, 13-CH<u>H</u>CH$_3$), 1.19 (s, 3 H, 12-CH$_3$), 1.43 (s, 3 H, 6-CH$_3$), 1.50 – 1.55 (m, 1 H, 13-CH<u>H</u>CH$_3$), 1.56 – 1.65 (m, 2 H, C<u>H</u>H-7/CH<u>H</u>-4'), 2.12 (s, 6 H, N(C<u>H</u>$_3$)$_2$), 2.26 – 2.31 (m, 1 H, H-4), 2.40 (pseudo t, 1 H, *J* 13.0, CH<u>H</u>-7), 2.46 – 2.51 (m, 1 H, H-3'), 2.52 – 2.59 (m, 1 H, H-8), 3.01 (dd, 1H, *J* 9.5, 8.0 Hz, H-2'), 3.14 – 3.21 (m, 1 H, H-2), 3.26 (d, 1 H, *J* 17.5 Hz, 10-C<u>H</u>HPh), 3.41 – 3.45 (m, 1 H, H-5'), 3.50 (d, 1 H, *J* 5.0 Hz, H-5), 4.00 (d, 1 H, *J* 17.5 Hz, 10-CH<u>H</u>Ph), 4.21 (d, 1 H, *J* 3.66 Hz, H-1'), 4.36 – 4.38 (m, 1 H, H-3), 4.91 (dd, 1 H, *J* 10.9, 1.7 Hz, H-13), 5.07 (s, 1 H, H-11), 7.17 – 7.22 (m, 1 H, Ar), 7-26 –7.30 (m, 4 H, Ar). ^{13}C NMR ($CDCl_3$): δ 10.3 (13-CH$_2$<u>C</u>H$_3$), 12.3 (8-Me), 12.7 (2-Me), 15.7 (4-Me), 21.2 (5'-Me), 22.8 (12-Me), 24.3 (13-<u>C</u>H$_2$CH$_3$), 27.6 (6-Me), 29.2 (C-4'), 33.0 (10-CH$_2$), 40.2 (C-8/N-Me$_2$), 43.1 (C-7), 43.6 (C-4), 45.9 (C-2), 65.3 (C-3'), 69.4 (C-5'), 69.6 (C-2'), 71.9 (C-3), 79.3 (C-13), 82.0 (C-6), 86.4 (C-5), 89.4 (C-12), 103.3 (C-1'), 120.3 (C-9), 126.0 (Ar), 128.3 (Ar), 129.4 (C-11), 129.5 (Ar), 140.1 (Ar), 144.5 (C-10), 179.5 (C-1). IR (film)) (CH_2Cl_2) ν = 3467 (br), 2972 (s), 2934 (m), 2876 (w), 1719 (s), 1455 (m), 1379 (m), 1321 (w), 1274 (w), 1169 (s), 1111 (m), 1097 (m), 1073 (s), 1050 (s), 1023(s), 992 (m), 906 (w).

10-(2-Furylmethyl)-10-desmethylerythralosamine (13).

A solution of 10-bromomethyl-10-desmethylerythralosamine *N*-oxide (4) (0.196 g, 0.310 mmol) in NMP (3 mL) was degassed and tris(2-furyl)phosphine (0.018 g, 0.077 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.010 g, 0.010 mmol) added. The reaction mixture was heated at 50 °C for 10 min and more tris(2-furyl)phosphine (0.12 mL, 0.372 mmol) added. The reaction mixture was heated at 80 °C for 22 h. The product was extracted with ethyl acetate, the organic phase washed with aqueous sodium hydrogen carbonate, brine and dried ($MgSO_4$). The NMP was removed under reduced pressure and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 90:4:1, yield 0.096 g (51%) of a white crystalline solid. HRMS: [M +1] 606.3654. Calc. for $C_{33}H_{51}NO_9$: 606.3636.

$O^{2',3}$-Bis(*t*-butyldimethylsilyl)-10 ethyl-10-desmethylerythralosamine (15).

A solution of 10-bromomethyl- $O^{2',3}$-bis(*t*-butyldimethylsilyl)-10-desmethylerythralosamine (5a)

(0.064 g, 0.080 mmol) in NMP (1 ml) was degassed for 1 h before tris(dibenzylideneacetone)dipalladium chloroform complex (0.002 g, 0.002 mmol) and tri(2-furyl)phosphine (0.004 g, 0.016 mmol) were added. The mixture was heated to 50 °C to generate the active catalyst and trimethylaluminum 2 M in hexane, (0.2 ml, 0.400 mmol)

added carefully through a syringe. The resultant reaction mixture was heated at 100 °C for 24 h. The cold reaction mixture was through a silica plug and the solvent was removed from the filtrate by distillation. The residual material was subjected to flash chromatography on silica gel using hexane:Et_2O 4:1; yield 0.053 g (84%) of a white crystalline material.

HRMS: [M+1], 782.5383. Calc. for $C_{42}H_{79}NO_8Si_2$: 782.5417. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03/0.05/0.07/0.19 (4 × s, 4 × 3 H, 2 × $(CH_3)_3C(C\underline{H}_3)_2$ Si), 0.84 (t, 3 H, *J* 7.4 Hz, 13-$CH_2C\underline{H}_3$), 0.88/0.90 (2 × s, 2 × 9 H, 2 × $(C\underline{H}_3)_3C(CH_3)_2$ Si), 0.92 (d, 3 H, *J* 7.2 Hz, 8-CH_3), 0.95 (d, 3 H, *J* 7.2 Hz, 4-CH_3), 1.06 (d, 3 H, *J* 7.5 Hz, 2-CH_3), 1.08 (t, 3H, 7.2 Hz, 10-$CH_2C\underline{H}_3$), 1.14 (d, 3 H, *J* 6.1 Hz, 5'-CH_3), 1.15 – 1.19 (m, 1 H, CH<u>H</u>-4'), 1.24 (s, 3 H, 12-CH_3), 1.32 – 1.35 (m, 1 H, 13-CH<u>H</u>CH_3), 1.47 (s, 3 H, 6-CH_3), 1.56 – 1.65 (m, 3 H, CH<u>H</u>-7/13-C<u>H</u>HCH_3/CH<u>H</u>-4'), 1.91 – 1.99 (m, 1H, C<u>H</u>H-10), 2.05 – 2.15 (m, 3 H, H-4/CH<u>H</u>-7/C<u>H</u>H-10), 2.18 (s, 6 H, $N(C\underline{H}_3)_2$), 2.40 – 2.43 (m, 1 H, H-3'), 2.44 – 2.54 (m, 2 H, H-8/H-2), 3.13 (m, 1 H, H-2'), 3.36 – 3.39 (m, 1 H, H-5'), 3.42 (d, 1 H, *J* 11.3 Hz, H-5), 4.05 (d, 1 H, *J* 7.1 Hz, H-1'), 4.22 (d, 1 H, *J* 4.9 Hz, H-3), 4.95 (dd, 1 H, *J* 11.6, 2.5 Hz, H-13), 5.45 (d, 1 H, Hz, H-11). ^{13}C NMR (300 MHz, $CDCl_3$): δ -4.4/-3.0 $(CH_3)_3C(\underline{C}H_3)_2Si$), 10.4 (13-$CH_2\underline{C}H_3$), 11.7 (4-Me), 11.9 (8-Me), 12.5 (10-$CH_2\underline{C}H_3$), 16.3 (2-Me), 18.5/18.6 $(CH_3)_3\underline{C}(CH_3)_2Si$), 20.4 (10-$\underline{C}H_2CH_3$), 21.2 (5'-Me), 23.4 (12-Me), 24.2 (13-$\underline{C}H_2CH_3$), 26.0/26.3 ($\underline{C}H_3)_3C(CH_3)_2Si$), 29.4 (C-4'), 30.3 (6-Me), 40.8 (C-8), 41.2 (N-Me_2), 43.5 (C-7), 48.1 (C-4), 50.8 (C-2), 66.2 (C-3'), 68.8 (C-5'), 70.1 (C-3), 72.1 (C-2'), 78.3 (C-13), 83.4 (C-6), 84.9 (C-5), 89.1 (C-12), 104.9 (C-1'), 120.3 (C-9), 125.2 (C-11), 145.5 (C-10), 178.5 (C-1).

10-(2-Ethoxyprop-2-en-1-yl)-10-desmethylerythralosamine (16).

10-Bromomethyl-10-desmethylerythralosamine *N*-oxide (**4**) (0.100 g, 0.158 mmol) was deoxygenated when a solution with tris(2-furyl)phosphine (0.036 g, 0.158 mmol) in NMP (1 ml) was heated at 70 °C for 17 h. The catalyst $Pd_2dba_3{\cdot}CHCl_3$ (0.005 g, 0.005 mmol) and tris(2-furyl)phosphine (0.009 g, 0.038 mmol) for the cross-coupling reaction were added to the reaction mixture together with tributyl(1-etoxyethenyl)stannane (0.064 ml, 0.189 mmol). The sesultant mixture was heated at 70 °C for 24 h. The solvent was removed at reduced pressure, the residue extracted into ethyl acetate, the solution shaken with aqueous sodium hydrogen carbonate, with brine, dried ($MgSO_4$), evaporated and the residual material subjected to flash chromatography on silica gel CH_2Cl_2:MeOH:NH_3 90:4:1; yield 0.052 g (54%) of a white crystalline material.

HRMS: [M+1], 610.3948. Calc. for $C_{33}H_{55}NO_9$: 6103949. ^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3 H, *J* 7.3 Hz, 13-$CH_2C\underline{H}_3$), 0.94 (d, 3 H, *J* 7.1 Hz, 8-CH_3), 1.07 (d, 3 H, *J* 3.2 Hz, 4-CH_3), 1.09 (d, 3 H, *J* 3.0 Hz, 2-CH_3), 1.19(d, 3 H, *J* 6.2 Hz, 5'-CH_3), 1.21 – 1.22 (m, 1 H, C$\underline{H}$H-4'), 1.24 (s, 3 H, 12-CH_3), 1.27 (t, 3H, *J* 7.1 Hz, $OCH_2C\underline{H}_3$), 1.28 – 1.32 (m, 1 H, 13-CH$\underline{H}$$CH_3$), 1.40 (s, 3 H, 6-$CH_3$), 1.56 (dd, 1 H, *J* 12.6, 6.5 Hz, C$\underline{H}$H-7), 1.60 – 1.66 (m, 1 H, H-4), 1.60 – 1.66 (m, 1 H, 13-CH$\underline{H}$$CH_3$), 2.26 – 2.30 (m, 1 H, H-4), 2.26 – 2.30 (m, 1H, C$\underline{H}$H-7), 2.30 (s, 6 H, $N(C\underline{H}_3)_2$), 2.42-2.55 (m, 1 H, 8-H) , 2.42 – 2.54 (m, 1 H, H-3'), 2.77 (dd, 1H, *J* 17.0, 1.8 Hz, H-10), 3.01 (dq, 1 H, *J* 7.5, 3.5 Hz, H-2), 3.24 (dd, 1 H, *J* 10.1, 7.4 Hz, H-2'), 3.41 (d, 1H, *J* 17.0 Hz, H-10), 3.41 – 3.45 (m, 1 H, H-5'), 3.48 (d, 1 H, *J* 5.5 Hz, H-5), 3.70-3.78 (m, 1 H, $CH_3C\underline{H}_2$-O), 3.97 (d, 1H, *J* 1.09 Hz, C$\underline{H}$H-?), 4.04 (s, 1 H, C$\underline{H}$H-?), 4.20 (d, 1 H, *J* 6.8 Hz, H-1'), 4.36 – 4.38 (m, 1 H, H-3), 4.91 (dd, 1 H, *J* 11.1, 2.9 Hz, H-13), 5.55 (s, 1 H, H-11). ^{13}C NMR ($CDCl_3$): δ 10.3 (13-$CH_2\underline{C}H_3$), 12.3 (8-Me), 12.7 (4-Me), 14.4 ($OCH_2\underline{C}H_3$) 15.4 (2-Me), 21.2 (5'-Me), 22.8 (12-Me), 24.5 (13-$\underline{C}H_2CH_3$), 27.9 (6-Me), 29.8 (C-4'), 33.4 (10-CH_2), 40.3 (C-8), 40.5 (N-Me_2), 43.2 (C-7/ C-4), 45.9 (C-2), 62.9 ($O\underline{C}H_2CH_3$), 64.8 (C-3'), 69.4 (C-5'), 70.1 (C-2'), 71.7 (C-3), 79.1 (C-13), 82.1 (C-6), 83.1 (=$\underline{C}H_2$), 85.9 (C-5), 89.3 (C-12), 103.3 (C-1'), 120.4 (C-9), 128.4 (C-11), 140.5 (C-10), 161.1 (EtO$\underline{C}$R=CH_2), 179.5 (C-1).
IR (ATR plate) ν:

C-10 Benzylaminomethyl-10-desmethylerythralosamine (30).

A solution of 10-bromomethyl-10-desmethylerythralosamine (**5**) (0.502 g, 0.812 mmol) and benzylamine (0.35 ml, 3.246 mmol) in DMF (4 ml) was heated at 60 °C for 16 h. Water was added to the cold reaction mixture, the mixture extracted with ethyl acetate, the extracts shaken with aqueos sodium hydrogen carbonate, with brine, dried ($MgSO_4$) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH: aq.NH_3 90:8:2; yield 0.40 g (78%) of a white crystalline solid, mp 151 – 152 °C.

HRMS: M, 645.4102. Calc. for $C_{29}H_{48}BrNO_8$: 645.4109. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3 H, *J* 7.3 Hz, 13-$CH_2C\underline{H}_3$), 0.88 (d, 3 H, *J* 7.0 Hz, 8-CH_3), 1.05 (d, 3 H, *J* 7.4 Hz, 4-CH_3), 1.08 (d, 3 H, *J* 7.4 Hz, 2-CH_3), 1.17 (d, 3 H, *J* 6.2 Hz, 5'-CH_3), 1.21 – 1.23 (m, 1 H, C$\underline{H}$H-4'), 1.26 (s, 3 H, 12-CH_3), 1.35 – 1.42 (m, 1 H, 13-CH$\underline{H}$$CH_3$), 1.39 (s, 3 H, 6-$CH_3$), 1.55 (dd, 1 H, *J* 12.7, 6.2 Hz, C$\underline{H}$H-7), 1.62 – 1.68 (m, 2 H, C$\underline{H}$H-4'/13-CH$\underline{H}$$CH_3$), 2.16 – 2.20 (m, 1 H, H-4), 2.22 – 2.26 (m, 1H, C$\underline{H}$H-7), 2.29 (s, 6 H, $N(C\underline{H}_3)_2$), 2.45 – 2.52 (m, 2 H, H-8/$\underline{H}$-3'), 2.76 – 2.82

(m, 1 H, H-2), 3.27 – 3.32 (m, 2 H, H-2'/CHH-10), 3.42 – 3.48 (m, 1 H, H-5'), 3.46 (d, 1 H, *J* 6.7 Hz, H-5), 3.63 (d, 1 H, *J* 16.3 Hz, CHH-10), 3.82 (d, 1 H, *J* 13.2 Hz, CHHPh), 3.92 (d, 1 H, *J* 13.2 Hz, CHHPh), 4.20 (d, 1 H, *J* 7.2 Hz, H-1'), 4.31 – 4.33 (m, 1 H, H-3), 4.96 (dd, 1 H, *J* 11.4, 2.7 Hz, H-13), 5.77 (s, 1 H, H-11). ^{13}C NMR ($CDCl_3$): δ 10.3 (13-CH_2CH_3), 12.3 (8-Me), 13.3 (2-Me), 14.3 (4-Me), 21.2 (5'-Me), 23.0 (12-Me), 24.4 (13-CH_2CH_3), 28.3 (6-Me), 29.4 (C-4'), 40.3 (C-8), 40.5 (N-Me_2), 43.1 (C-7), 44.2 (C-4), 45.7 (10-H_2), 46.6 (C-2), 52.7 (cH_2Ph), 65.3 (C-3'), 69.4 (C-5'), 70.1 (C-2'), 71.1 (C-3), 79.1 (C-13), 82.2 (C-6), 85.9 (C-5), 89.3 (C-12), 103.8 (C-1'), 120.0 (C-9), 126.8 (ar), 128.0 (C-11), 128.1 (ar), 128.4 (ar), 140.3 (ar), 141.9 (C-10), 178.9 (C-1). IR (film)) (CH_2Cl_2) v = 3454 (m), 2972 (s), 2934 (s), 2876 (m), 1722 (s), 1455 (s), 1380 (m), 1323 (w), 1278 (w), 1171 (s), 1111 (s), 1097 (s), 1074 (s), 1049 (s), 1025(s), 993 (m), 905 (m).

10-(*p*-Chloroanilinomethyl-10-desmethylerythralosamine *N*-Oxide (31).

A solution of 10-bromomethyl-10-desmethylerythralosamine *N*-oxide (4) (0.613 g, 0.968 mmol) and *p*-chloroaniline (0.540 g 3.872 mmol) in NMP (5 mL) was heated at 100 °C for 20 h. Water was added to the cold reaction mixture, the mixture extracted with ethyl acetate, the extracts shaken with aq. sodium hydrogen carbonate, with brine, the solution dried ($MgSO_4$) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:aq.NH_3 90:4:1; yield 0.129 g (20 %) of a white crystalline material, mp ?? °C.

HRMS: [M +1], 665.3547. Calc. for $C_{35}H_{53}NO_8Cl$: 665.3547. ^{1}H NMR ($CDCl_3$): δ 0.78 (t, 3 H, *J* 7.3 Hz, 13-CH_2CH_3), 0.99 (d, 3 H, *J* 7.1 Hz, 8-CH_3), 1.05-1.08 (m, 1 H, CHH-4'), 1.12 (d, 3 H, *J* 4.8 Hz, 2-CH_3), 1.13 (d, 3 H, *J* 4.8 Hz, 4-CH_3), 1.18 (d, 3 H, *J* 6.1 Hz, 5'-CH_3), 1.21 – 1.23 (m, 1 H, 13-CHHCH$_3$), 1.24 (s, 3 H, 12-CH_3), 1.40 (s, 3 H, 6-CH_3), 1.53 – 1.60 (m, 3 H, CHH-7/CHH-4' /13-CHHCH$_3$), 2.09 (s, 6 H, N(CH_3)$_2$), 2.24 – 2.25 (m, 1 H, H-4), 2.29 (pseudo t, 1H, *J* 13.0 Hz, 7-CHH), 2.39 – 2.44 (m, 1 H, H-3'), 2.47 – 2.55 (m, 1 H, H-8), 3.08 (dq, 1 H, *J* 10.3, 7.4 Hz, H-2'), 3.10 – 3.13 (m, 1 H, H-2), 3.42-3.47 (m, 1 H, H-5'), 3.48 (d, 1 H, *J* 4.6 Hz, H-5), 3.78 (dd, 1H, *J* 17.4, 5.0 Hz, CHH-10), 4.18 (t, 1H, *J* 5.8 Hz, NH), 4.23 (d. 1 H, *J* 7.4 Hz, H-1'), 4.34 (dd, 1 H, *J* 17.4, 4.5 Hz, CHH-10), 4.42 – 4.44 (m, 1 H, H-3), 4.92 (dd, 1 H, *J* 11.3, 2.8 Hz, H-13), 5.70 (s, 1 H, H-11), 6.63 (d(AA'BB'), 2 H, *J* 8.8, ar.), 7.06, (d(AA'BB'), 2 H, *J* 8.8, ar.). ^{13}C NMR ($CDCl_3$): δ 10.2 (13-CH_2CH_3), 12.4 (8-Me), 12.6 (4-Me), 16.2 (2-Me), 21.3 (5'-Me), 22.8 (12-Me), 24.4 (C-14), 27.3 (6-Me), 28.5 (C-4'), 40.0 (C-

8), 40.1 (*N*-Me_2), 41.8 (10-CH_2), 42.9 (C-7), 43.5 (C-4), 45.6 (C-2), 65.6 (C-3'), 69.5 (C-5'), 69.6 (C-2'), 71.7 (C-3), 79.1 (C-13), 81.9 (C-6), 86.4 (C-5), 89.4 (C-12), 103.6 (C-1'), 114.3 (ar.), 119.8 (C-9), 121.6 (ar.-Cl), 128.5 (C-11), 128.8 (ar.), 141.8 (C-10), 146.8 (ar.-NH), 179.5 (C-1).

IR (ATR plate) v:

11 Hydroxy-$O^{2',3}$-bis(trimethylsilyl)erythralosamine *N*-oxide (37).

$O^{2',3}$-Bis(trimethylsilyl) erythralosamine (**2a**) (0.409g, 0.598 mmol) was dissolved in a borane-methyl sulfide complex in THF (2 M, 3 ml, 5.978 mmol) and the mixture stirred at ambient temperature for 17 h. Ethanol (0.5 ml) and 1 M sodium hydroxide (0.5 ml) were added to the resultant reaction mixture which was cooled to 0 °C before addition of hydrogen (30%, 2 ml). Stirring was continued for 2 h, the mixture extracted with ethyl acetate, the extracts shaken with sodium hydrogen carbonate, brine, dried ($MgSO_4$), and evaporated. The residual material was subjected to flash chromatography on silica gel using hexane:Et_2O 1:1; yield 0.144 g (35%) of a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.13/0.20 (2 × s, 2 × 9 H, $Si(CH_3)_3$), 0.84 (t, 3 H, *J* 7.3 Hz, 13-$CH_2C\underline{H}_3$), 0.90 (d, 3 H, *J* 7.3 Hz, 4-CH_3), 0.99 (d, 3 H, *J* 6.6 Hz, 10-CH_3), 1.00 (d, 3 H, *J* 6.9 Hz, 8-CH_3), 1.07 (d, 3 H, *J* 7.3 Hz, 2-CH_3), 1.12 (s, 3 H, 12-CH_3), 1.17 (d, 3 H, *J* 6.2 Hz, 5'-CH_3), 1.40 – 1.45 (m, 1 H, 13-C$\underline{H}$HCH$_3$), 1.43 (s, 3 H, 6-CH_3), 1.53 – 1.60 (m, 3 H, C$\underline{H}$H-7/13-CH$\underline{H}$CH$_3$)/CH$\underline{H}$-4'), 1.88 (pseudo t, 1 H, *J* 12.6 Hz, C$\underline{H}$H-7), 1.91 – 1.94 (m, 1 H, H-10), 2.34 – 2.37 (m, 1 H, C$\underline{H}$H-4'), 2.49 – 2.58 (m, 3 H, H-4/H-2/CH$\underline{H}$-7), 2.26 (s, 3 H, N(C$\underline{H}_3$), 2.75 (s, 3 H, N(CH_3), 2.77 – 2.80 (m, 1 H, H-3'), 3.45 (d, 1 H, *J* 11.1 Hz, H-5), 3.44 – 3.50 (m, 1 H, H-5'), 3.84 (dd, 1 H, *J* 8.6, 7.3 Hz, H-2'), 4.10 (d, 1 H, *J* 6.7 Hz, H-1'), 4.34 – 4.38 (m, 2 H, H-3/H-11), 4.96 (dd, 1 H, *J* 11.4, 3.0 Hz, H-13). ^{13}C NMR ($CDCl_3$): δ 0.6/1.4 ($Si(CH_3)_3$, 10.1 (13-$CH_2\underline{C}H_3$), 11.9 (4-Me), 13.7 (10-Me), 15.0 (8-Me), 16.1 (2-Me), 20.4 (12-Me), 21.0 (5'-Me), 24.0 (13-$\underline{C}H_2CH_3$), 29.1(6-Me), 35.0 (C-4'), 40.5 (C-8), 45.4 (C-4), 45.5 (C-7), 46.5 (C-10), 48.6 (N-Me), 49.7 (C-2), 54.5 (N-Me), 68.5 (C-5'), 69.8 (C-3), 70.5 (C-3'), 74.5 (C-2'), 77.4 (C-11), 78.5 (C-13), 83.4 (C-6), 84.7 (C-5), 85.5 (C-12), 103.9 (C-1'), 112.9 (C-9), 177.3 (C-1)

10,11-Epoxyerythralosamine *N*-oxide (40).

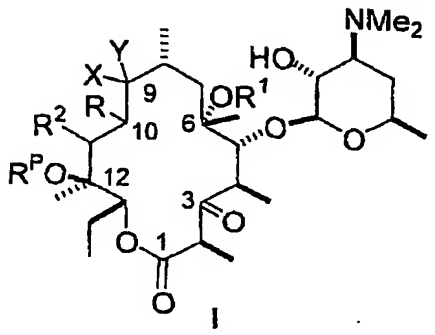
A solution of erythralosamine (0.573 g, 1.062 mmol) and MCPBA (1.66 g, 7.432 mmol) in dichloromethane (20 ml) was heated under reflux for 4 h, another portion of MCPBA added (0.55 g, 3.186 mmol) and the heating continued for another 4 h. Sodium hydrogen carbonate was added to the cold mixture, stirred overnight and extracted with dichloromethane. The organic phase was washed with Na_2SO_3, brine and dried ($MgSO_4$). The crude product was purified by flash chromatography (silica gel) CH_2Cl_2:MeOH 9:1; yield 0.298 g, (49%) of a white crystalline material, mp ? HRMS: M, 572.3429. Calc. for $C_{29}H_{49}NO_9$: 572.3456. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3 H, *J* 6.9 Hz, 13-$CH_2C\underline{H}_3$), 1.15 (d, 3 H, *J* 7.2 Hz, 8-CH_3), 1.18 (s, 3 H, 10-CH_3), 1.18 – 1.22 (m, 9 H, 4-CH_3/2-CH_3/5'-CH_3), 1.28 (s, 3 H, 6-CH_3), 1.31 – 1.36 (m, 1 H, C$\underline{H}$H-4'), 1.46 – 1.49 (m, 1H, 13-C$\underline{H}$HCH$_3$) 1.51 (dd, 1 H, *J* 12.4, 6.8 Hz, C$\underline{H}$H-7), 1.61 (s, 3 H, 12-CH_3), 1.64 – 1.70 (m, 1 H, 13-CH$\underline{H}$CH$_3$), 1.90 – 1.93 (m, 1 H, CH$\underline{H}$-4'), 2.17 – 2.23 (pseudo t, 1 H, *J* 12.7 Hz, CH$\underline{H}$-7), 2.45 – 2.56 (m, 2 H, H-8/H-4), 3.04 – 3.10 (m, 1 H, H-2), 3.13 (s, 3 H, NCH_3), 3.16 (s, 3 H, NCH_3), 3.30 (s, 1 H, H-11), 3.37 – 3.41 (m, 1 H, H-3'), 3.48 (d, 1 H, *J* 6.1 Hz, H-5), 3.56 – 3.58 (m, 1 H, H-5'), 3.65 (dd, 1 H, *J* 9.9, 7.2 Hz, H-2'), 4.03 (pseudo t, 1 H, *J* 5.3 Hz, H-3), 4.36 (d. 1 H, *J* 7.1 Hz, H-1'), 4.91 (dd, 1 H, H-13). ^{13}C NMR ($CDCl_3$): δ 10.1 (13-$CH_2\underline{C}H_3$), 13.8 (8-Me), 14.6 (2-Me), 15.1 (12-Me), 16.8 (4-Me), 19.0 (10-Me), 20.9 (5'-Me), 24.5 (13-$\underline{C}H_2CH_3$), 25.6 (6-Me), 34.8 (C-4'), 39.8 (C-8), 44.1 (C-7/C-4), 46.0 (C-2), 52.2 (NMe), 59.1 (NMe), 63.7 (C-11), 65.4 (C-10), 67.7 (C-5'), 71.3 (C-2'), 73.5 (C-3), 76.1 (C-3'), 78.7 (C-13), 83.3 (C-12), 83.7 (C-6), 85.2 (C-5), 102.3 (C-1'), 113.5 (C-9), 178.5 (C-1).

10,11-Epoxyerythralosamine (41).

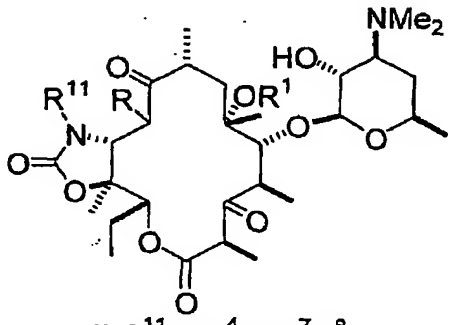
A solution of 10,11-Epoxyerythralosamine *N*-oxide (37) (0.380 g, 0.665 mmol) and triphenylphosphine (0.350 g, 1.33 mmol) in THF (5 ml) was heated at reflux for 17 h. Most of the THF was removed by distillation, the residual material extracted into ethyl acetate, the extracts shaken with aqueous sodium bicarbonate, washed with brine and dried ($MgSO_4$). The solution was evaporated and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 90:8:2; yield 0.216 g (60%) of a white crystalline material. HRMS: M 556.3474. Calc. for $C_{29}H_{49}NO_9$: 556.3480.

Claims

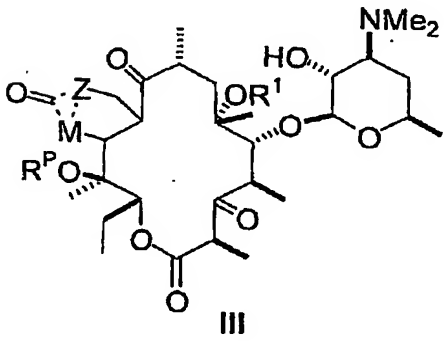
1. A compound having a formula chosen among the group consisting of I, II, III, and IV,



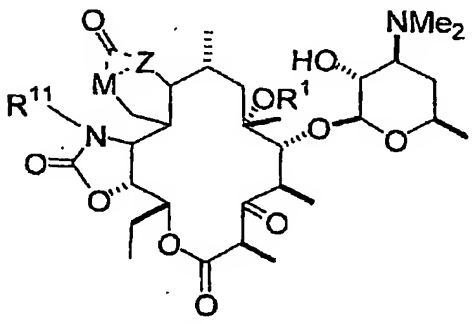
I



II $R^{11} = R^4, NR^7R^8$



III



IV $R^{11} = R^4, NR^7R^8$

or being a salt, ester or prodrug thereof, wherein

R is selected from the group consisting of

(1) methyl substituted with one or more substituents selected from the group consisting of

(i) CN,

(ii) F,

(iii) CO_2R^3 wherein R^3 is selected from hydrogen, C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl, or heteraryl substituted C_1-C_3-alkyl,

(iv) OR^4 wherein R^4 is selected from hydrogen, C_1-C_4-alkyl or aryl substituted C_1-C_4-alkyl, or heteraryl substituted C_1-C_4-alkyl, heterocycloalkyl and optionally

substituted cycloalkyl, C_1-C_3-alkoxy-C_1-C_3-alkoxy, C_1-C_4-alkenyl or aryl substituted C_1-C_4-alkenyl, or heteraryl substituted C_1-C_4-alkenyl, heterocycloalkyl and optionally substituted cycloalkyl, aryl or optionally substituted aryl, heteroaryl or optionally substituted heteroaryl,

(v) $S(O)_nR^3$ where n = 0, 1 or 2 and R^3 is as previously defined

(vi) $NR^4C(O)R^3$ wherein R^3 and R^4 are as previously defined

(vii) $NR^4C(O)NR^5R^6$ wherein R^4 is defined as defined previously, and R^5 and R^6 are independently selected from hydrogen, C_1-C_3-alkyl, C_1-C_3 alkyl substituted with aryl, substituted aryl, heteroaryl, substituted heteroaryl

(viii) NR^7R^8 wherein R^7 and R^8 are independently selected from the group consisting of

(a) hydrogen

(b) C_1-C_{12}-alkyl, and optionally substituted C_1-C_{12}-alkyl

(c) C_1-C_{12}-alkenyl, and optionally substituted C_1-C_{12} alkenyl

(d) C_1-C_{12}-alkynyl, and optionally substituted C_1-C_{12}-alkynyl

(e) aryl, and optionally substituted aryl

(f) heteroaryl, and optionally substituted heteroaryl

(g) heterocycloalkyl, and optionally substituted heterocycloalkyl

(h) C_1-C_{12} alkyl substituted with aryl, and optionally substituted with substituted aryl

(i) C_1-C_{12} alkyl substituted with heteroaryl, and optionally substituted with substituted heteroaryl

(j) C_1-C_{12}-alkyl substituted with heterocycloalkyl, and with optionally substituted heterocycloalkyl, and

(k) R^7 and R^8 taken together with the atom to which they are attached form a 3-10-membered heterocycloalkyl ring which may cointain one or more additional heteroatoms and may be substituted with one or more substituents independently selected from the group consisting of

(aa) halogen, hydroxy, C_1-C_3-alkoxy, alkoxy-C_1-C_3-alkoxy, oxo, C_1-C_3-alkyl, aryl and optionally substituted aryl, heteroaryl and optional substituted heteroaryl

(bb) CO_2R^3 wherein R^3 is as previously defined, and

(cc) $C(O)NR^5R^6$ wherein R^5 asnd R^6 are as previously defined,

(ix) aryl, and optionally substituted aryl, and

(x) heteroaryl, and optionally substituted heteroaryl,

(2) C_2-C_{10}-alkyl,

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of

(i) halogen,

(ii) OR^4 wherein R^4 is as defined previously

(iii) –CHO,

(iv) oxo,

(v) NR^7R^8 wherein R^7 and R^8 are defined as previously

(vi) =N-O-R^4 is wherein R^3 is as previously defined

(vii) –CN

(viii) -$S(O)_nR^3$ wherein n = 0, 1 or 2 and R^3 is as previously defined

(ix) aryl, and optionally substituted aryl

(x) heteroaryl, and optionally substituted heteroaryl

(xi) C_3-C_8-cycloalkyl, and optionally substituted C_3-C_8-cycloalkyl

(xii) heterocycloalkyl, and optionally substituted cycloalkyl

(xiii) $NR^4C(O)R^3$ where R^3 and R^4 are as previously defined

(xiv) $NR^4C(O)NR^5R^6$ wherein R^4, R^5 and R^6 are as previously defined

(xv) =N-NR^7R^8 wherein R^7 and R^8 are as previously defined

(xvi) =N-R^4 wherein R^4 is as previously defined

(xvii) =N-$N^4C(O)R^3$ wherein R^3 and R^4 are as previously defined, and

(xviii) =N-$NR^4C(O)NR^5R^6$ wherein R^4, R^5 and R^6 are as previously defined,

(4) C_1-C_{10}-alkenyl,

(5) C_1-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of

(i) halogen,

(ii) OR^4 wherein R^4 is as previously defined

(iii) O-$S(O)_nR^3$ where R^3 is as previously defined

(iv) –CHO,

(v) oxo,

(vi) -CO_2R^3 where R^3 is as previously defined

(vii) –C(O)-R^4 where R^4 is as previously defined

(viii) –CN

(ix) aryl, and optionally substituted aryl

(x) heteroaryl, and optionally substituted heteroaryl

(xi) C_3-C_7-cycloalkyl

(xii) C_1-C_{12}-alkyl substituted with heteroaryl

(xiii) NR^7R^8 wherein R^7 and R^8 are as previously defined

(xiv) $NR^4C(O)R^3$ where R^3 and R^4 are as previously defined

(xv) $NR^4C(O)NR^5R^6$ where R^4, R^5 and R^6 are as previously defined

(xvi) $=N\text{-}O\text{-}R^4$ where R^4 is as previously defined

(xvii) $=N\text{-}NR^7R^8$ wherein R^7 and R^8 are as previously defined

(xviii) $=N\text{-}NR^4$ wherein R^4 is as previously defined

(xix) $=N\text{-}NR^4C(O)R^3$ wherein R^3 and R^4 are as previously defined, and

(xx) $=N\text{-}NR^4C(O)NR^5R^6$ wherein R^4, R^5 and R^6 are as previously defined,

(6) C_2-C_{10}-alkynyl

(7) C_2-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of

(i) trialkylsilyl

(ii) halogen

(iii) –CN

(iv) OR^4 where R^4 is defined as previously

(v) –CHO

(vi) oxo

(vii) $-CO_2R^3$ where R^3 is as previously defined

(viii) $-C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined

(ix) NR^7R^8 wherein R^7 and R^8 are as previously defined

(x) $O\text{-}S(O)_nR^3$ where R^3 is as previously defined

(xi) C_3-C_7-cycloalkyl

(xii) C_1-C_{12}-alkyl substituted with heteroaryl

(xiii) aryl, and optionally substituted aryl

(xiv) heteroaryl, and optionally substituted heteroaryl

(xv) $NR^4C(O)R^3$ where R^3 nd R^4 are as previously defined

(xvi) $NR^4C(O)NR^5R^6$ where R^4, R^5 and R^6 are as previously defined

(xvii) $=N\text{-}O\text{-}R^4$ where R^4 is as previously defined

(xviii) $=N\text{-}NR^7R^8$ wherein R^7 and R^8 are as previously defined

(xix) $=N-NR^4C(O)R^3$ where R^3 and R^4 are as previously defined, and

(xxi) $=N-NR^4C(O)NR^5R^6$ wherein R^4, R^5 and R^6 are as previously defined,

(8) cyclic substituents

(i) aryl, and optionally substituted aryl

(ii) heteroaryl, and optionally substituted heteroaryl

(iii) heterocycloalkyl, and optionally substituted heterocycloalkyl, and

(iv) C_3-C_7-cycloalkyl, and optionally substituted C_3-C_7-cycloalkyl, and

(9) C_1 substituents with the exception of 10-methyl derivatives which are part of the above definitions under (1)

(i) –CHO

(ii) –CN

(iii) CO_2R^3 wherein R^3 is as previously defined

(iv) $C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined

(v) $C(S)NR^5R^6$ wherein R^5 and R^6 are as previously defined

(vi) $C(NR^4)NR^5NR^6$ where R^4, N^5 and R^6 are as previously defined

(vii) $CH=N-O-R^4$ is wherein R^4 is as previously defined

(viii) $CH=N-R^4$ wherein R^4 is as previously defined

(ix) $CH=N-NR^7R^8$ wherein R^7 and R^8 are as previously defined

(x) $CH=N-NR^4C(O)R^3$ where R^3 and R4 are as previously defined, and

(xi) $CH=N-NR^4C(O)NR^5R^6$ wherein R^4, R^5 and R^6 are as previously defined;

R^1 is selected from the group consisting of

(1) H

(2) methyl

(3) methyl substituted with one or more substituents selected from the group consisting of

(i) F

(ii) –CN

(iii) $–CO_2R^{11}$ where R^{11} is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl, or heteroalkyl substituted C_1-C_3-alkyl

(iv) $–C(O)NR^5R^6$ where R^5 and R^6 are defined as previously

(v) aryl, and optionally substituted aryl, and

(vi) heteroaryl, and optionally substituted heteroaryl,

(4) C_2-C_{10}-alkyl

(5) substituted C_2-C_{10}-alkyl with one or more substituents selected from the group consisting of

(i) halogen

(ii) OR^4 where R^4 is defined as previously

(iii) C_1-C_3-alkoxy-C_1-C_3-alkoxy

(iv) –CHO

(v) oxo

(vi) NR^7R^8 wherein R^7 and R^8 are as defined previously

(vii) $=N\text{-}O\text{-}R^4$ is wherein R^4 is as previously defined

(viii) –CN

(ix) $-S(O)_nR^3$ wherein n = 0, 1 or 2 and R^3 is as previously defined

(x) aryl, and optionally substituted aryl

(xi) heteroaryl, and optionally substituted heteroaryl

(xii) C_3-C_8-cycloalkyl, and optionally substituted C_3-C_8-cycloalkyl

(xiii) C_1-C_{12}-alkyl substituted with heteroaryl, and optionally substituted heteroaryl

(xiv) heterocycloalkyl

(xv) $NHC(O)R^3$ where R^3 is as previously defined

(xvi) $NHC(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined

(xvii) $=N\text{-}NR^7R^8$ wherein R^7 and R^8 are as previously defined

(xviii) $=N\text{-}R^4$ wherein R^4 as previously defined, and

(xix) $=N\text{-}NHC(O)R^3$ wherein R^3 is 5and R^6 are as previously defined,

(4) C_1-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of

(i) halogen

(ii) OR^4 where R^4 is as previously defined

(iii) –CHO

(iv) oxo

(v) $O\text{-}S(O)_nR^3$ where R^3 is as previously defined

(vi) –CN

(vii) $-CO_2R^3$ where R^3 is as previously defined

(viii) NR^7R^8 wherein R^7 and R^8 are as previously defined

(ix) $=N\text{-}O\text{-}R^4$ where R^4 is as previously defined

(x) $-C(O)\text{-}R^4$ where R^4 is as previously defined

(xi) $-C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined

(xii) aryl, and optionally substituted aryl

(xiii) heteroaryl, and optionally substituted heteroaryl

(xiv) C_3-C_7-cycloalkyl

(xv) C_1-C_{12}-alkyl substituted with heteroaryl

(xvi) $NHC(O)R^3$ where R^3 is as previously defined

(xvii) $NHC(O)NR^5R^6$ where R^5 and R^5 are as previously defined

(xviii) $=N-NR^7R^8$ wherein R^7 and R^7 are as previously defined

(xix) $=N-NR^4$ wherein R^4 is as previously defined

(xx) $=N-NHC(O)R^3$ where R^3 is as previously defined, and

(xxi) $=N-NHC(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined,

(5) C_1-C_{10}-alkynyl, and

(6) C_1-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of

(i) halogen

(ii) OR^4 where R^4 is as previously defined

(iii) –CHO

(iv) oxo

(v) $-CO_2R^3$ where R^3 is as previously defined

(vi) $-C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined

(vii) –CN

(viii) NR^7R^8 wherein R^7 and R^8 are as previously defined

(ix) $=N-O-R^4$ where R^4 is as previously defined

(x) $O-S(O)_nR^3$ where R^3 is as previously defined

(xi) aryl, and optionally substituted aryl

(xii) heteroaryl, and optionally substituted heteroaryl

(xiii) C_3-C_7-cycloalkyl

(xiv) C_1-C_{12}-alkyl substituted with heteroaryl

(xv) $NHC(O)R^3$ where R^3 is as previously defined

(xvi) $NHC(O)NR^5R^6$ where R^5 and R^6 are as previously defined

(xvii) $=N-NR^7R^8$ wherein R^7 and R^8 are as previously defined

(xviii) $=N-NR^9$ wherein R^9 is as previously defined

(xix) $=N-NHC(O)R^3$ where R^3 is as previously defined, and

(xx) =N-NHC(O)NR^5R^6 wherein R^5 and R^6 are as previously defined;

R^2 is selected from the group consisting of

(1) hydrogen

(2) OH

(3) OR^3 where R^3 is as previously defined

(4) $OC(O)R^3$ where R^3 is as previously defined, and

(5) $O(CO)OR^3$ where R^3 is as previously defined;

and X and Y taken together are selected from the group consisting of

(1) O

(2) NOR^4 wherein R^4 is as defined previously

(3) N-O $C(R^9)(CR^{10})$-O-R^4 where R^4 is as previously defined and

(i) R^9 and R^{10} are each independently defined as R^4, or

(ii) R^9 and R^{10} taken together with the atom to which they are attached form a C_3-C_{12} cycloalkyl ring,

(4) NR^4 wherein R^4 is as previously defined, and

(5) N-NR^7R^8 wherein R^7 and R^8 are as previously defined,

or one of X and Y is hydrogen and the other is selected from the group consisting of

(1) -OR^4 wherein R^4 is as previously defined, and

(2) -NR^7R^8 wherein R^7 and R^8 are as previously defined.

R^p is selected from the group consisting of

(1) hydrogen

(2) R^3 as previously defined

(3) COR^3 where R^3 is as previously defined;

subject to the proviso that when the structure is III, Z and M are part of a five- or six-membered ring, said rings optionally being fully or partially unsaturated; for the six-membered ring, the bonding between Z and M is through a carbonyl group; for the five-membered ring, the bonding is directly between Z and M excluding CO; Z and M are independently selected from the group consisting of carbon, oxygen or N; and when M = N a second bridge may exist between this nitrogen and the oxygen of the 12-OH group whereby either an additional annulated oxazole or oxazine ring constitutes part of the molecule;

and subject to the proviso that when the structure is IV, Z and M are part of a five- or six-membered ring, said rings optionally being fully saturated or fully or partially unsaturated; for the six-membered ring, the bonding between Z and M is through a carbonyl group; for the

five-membered ring, the bonding is directly between Z and M excluding CO; Z and M are independently selected from the group consisting of carbon, oxygen or nitrogen; and when M = N a second bridge may exist between this nitrogen and the urethane nitrogen.

2. Intermediate for the manufacture of a compound according to claim 1, said intermediate being a derivative of erythrolosamine and in particular an erythromycin ketolide characterized in having an R substituent comprising a halogeno derivative, preferably a halogenoalkyl, more preferred chloromethyl, bromomethyl, iodomethyl, most preferred bromomethyl.

3. Intermediate for the manufacture of a compound according to claim 1, said intermediate having a formula chosen among the group consisting of 3, 4, 5, 5a, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, and 66; preferably chosen among the group consisting of 3, 4, 5, 5a, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 29, 30, 31, 32, 33, and 37.

4. Process for manufacturing a compound according to claim 1-3, comprising the steps of

(a) protection of the nitrogen in the amino group in structure 2, preferably by oxidation,

(b) halogenation, preferably bromination,

(c) deprotection of said amino group,

and optionally further comprising

(d) protection of OH-groups, preferably as a silyl ether.

5. Process for manufacturing a compound according to claim 1-3, comprising the steps of

(e) selective protection of the 2'-OH group, preferably using acetic anhydride with triethylamine,

(f) oxidation, preferably Corey-Kim oxidation,

(g) deprotection of the 2'-OH group,

(h) oxidation and bromination.

6. Process for manufacturing a compound according to claim 1-3, comprising the step of
(i) cross-coupling of a compound of formula **4** or **5**.

7. Process for manufacturing a compound according to claim 1-3, comprising the step of
(j) reacting trimethylaluminum with a compound of formula **5a** under palladium-mediated catalysis.

8. Process for manufacturing a compound according to claim 1-3, comprising the step of
(k) introducing a functionalized alkene in a compound of formula **4**, preferably under Stille conditions.

9. Process for manufacturing a compound according to claim 1-3, comprising the step of
(l) performing acid catalysed cleavage of the vinyl ether of a compound of formula **16** for obtaining a methyl ketone.

10. Process for manufacturing a compound according to claim 1-3, comprising the step of
(m) providing a hydroxymethyl derivative by subjecting a compound of formula **4** or **5** to hydrolytic conditions.

11. Use of a compound or intermediate according to claim 1-3, for the manufacture of a medicament, preferably for the treatment or prevention of infection in mammals.

12. Pharmaceutical composition comprising a compound or intermediate, according to claim 1-3, in a pharmaceutically acceptable form, said composition optionally further comprising at least one pharmaceutical excipient.

Title:

10-Substituted Erythromycin Ketolides and Methods of Making.

Abstract

The present application concerns a new class of macrolide compounds having a novel modification in the C-10 position and provides a new class of 10-substituted 10-desmethyl ketolide derivatives.

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